REveAL^{TM} and CARElink^{TM} (Real Care): Minimising the time taken to achieve a diagnosis in the implantable loop recorder population

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For Niki and Isabelle

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Abbreviations

ACC	American College of Cardiology
AF	Atrial Fibrillation
AMED	Allied and Complementary Medicine
AT	Atrial Tachycardia
AV	Atrio-Ventricular
AVB	Atrio-Ventricular Block
AVNRT	AV Nodal Re-entrant Tachycardia
BAGH	Bishop Auckland General Hospital
BBB	Bundle Branch Block
BCT	Broad Complex Tachycardia
BHRS	British Heart Rhythm Society
BNI	British Nursing Index
bpm	Beats Per Minute
Cath Lab	Catheterisation Laboratory
CCRI	Centre for Clinical Research and Innovation
CDDFT	County Durham and Darlington NHS Foundation Trust
CI	Chief Investigator
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CONSORT	Consolidated Standards of Reporting Trials
CRM	Cardiac Rhythm Management
CRT	Cardiac Resynchronisation Therapy
CSM	Carotid Sinus Massage
DMH	Darlington Memorial Hospital
ECG	Electrocardiograph
Echo	Echocardiogram or Echocardiography

EMBASE	Excerpta Medica Database
EP	Electrophysiological
ESC	European Society of Cardiology
FVT	Fast Ventricular Tachycardia
GCP	Good Clinical Practice
GTN	Glyceryltrinitrate
HMIC	Health Management Information Consortium
HOCM	Hypertrophic Obstructive Cardiomyopathy
HR	Heart Rate
HR	Hazard Ratio
HRUK	Heart Rhythm United Kingdom
HUT	Head Up Tilt
ICD	Implantable Cardioverter Defibrillator
IG	Information Governance
ILR	Implantable Loop Recorder
ISSUE	International Study on Syncope of Uncertain Etiology
LBNP	Lower Body Negative Pressure
NCT	Narrow Complex Tachycardia
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMS	Neurally Mediated Syncope
NSR	Normal Sinus Rhythm
OH	Orthostatic Hypotension
p	Probability
PAG	Patient Advisory Group

PICTURE	Place of Reveal™ in the Care Pathway and Treatment of Patients with Unexplained Recurrent Syncope
PII	Patient Identifiable Information
PIS	Patient Information Sheet
PM	Pacemaker
PULSE	The pilot study of the Sleuth® implantable ECG monitoring system
QoL	Quality of Life
RCT	Randomised Controlled Trial
RF	Radio Frequency
SA	Sinoatrial
SD	Standard Deviation
SND	Sinus Node Dysfunction
SPSS	Statistical Package for the Social Sciences
SSS	Sick Sinus Syndrome
SVT	Supraventricular Tachycardia
TLoC	Transient Loss of Consciousness
TTE	Time to Event
UHND	University Hospital of North Durham
UK	United Kingdom
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

Abstract

Introduction

Syncope accounts for ≈ 2.7/1000 population/year of presentations to UK healthcare, a figure believed to be underestimated by up to 30% due to misdiagnosis. For some patients the cause of their episode/s may remain unexplained.

The implantable loop recorder (ILR) is effective for diagnosis of syncope and palpitations, with UK and European guidelines advising its use if symptoms are infrequent. However current follow-up regimes can lead to a slow diagnostic pathway for patients. Remote monitoring technology allows patients to send their ILR data to their clinic

Research Questions

1) Does remote monitoring of ILRs reduce time to diagnosis and/or increase diagnostic yield?

2) What is the impact of remote monitoring on logged events requiring analysis?

Method

New ILR patients at a single implanting centre were recruited. Following informed consent, they were randomised into control or experimental groups. Patients in the control group were reviewed in the conventional manner with routine 6 monthly follow-ups plus additional ad hoc checks if

symptoms occurred. Patients in the experimental group were asked to send transmissions fortnightly or following a symptom.

All recordings were reviewed and classified as true or false events according to pre-defined criteria. Significant true event ECGs were reviewed blindly by a cardiologist. All data were verified by two physiologists or a physiologist and a cardiologist prior to analysis. The primary outcome variable was median time to clinical diagnosis.

Results

37 patients were randomised, 19 to the control and 18 to the experimental group. The control group comprised 11 males and 8 females with a median age of 60 (36-86) years. The experimental group comprised 10 males and 8 females, median age 58 (36-84) years. Mann-Whitney U testing showed no significant differences in group demographics.

Following randomisation 5526 events were logged, 1264 in the control and 4262 in the experimental group. 28 (76%) of patients had a true event, which led to a diagnosis in 23 (67%) of patients. There were 13 patients with true events and 10 diagnoses in the experimental group, with 15 true events and 13 diagnoses in the control group. Asystole was the most common event that led to a diagnosis, accounting for 35% of diagnoses.

Kaplan-Meier analysis was used to assess the primary outcomes of time from event to follow-up, and time to clinical diagnosis. Compared to the control group, the median time from event to follow-up was reduced from 3 to 1 week

(p=0.004). Median time to diagnosis was reduced from 13 to 6 weeks (p=0.049) when remote monitoring was used.

Conclusion

In patients with ILR, remote monitoring significantly reduced diagnostic delay although the overall diagnostic yield was not increased. However remote monitoring resulted in a three-fold increase in logged events that required analysis with only 1 in 328 proving to be true events: this will have significant resource implications.

Chapter 1. Introduction: The need and rationale for this research

For some patients, despite the best efforts of all healthcare professionals involved it can still take a long time to receive a diagnosis for the cause of their symptoms. The following thesis will present the REveAL™ and CARElink™ (Real Care) study which aimed to ascertain if this time lag could be significantly reduced for a cohort of patients affected by unexplained syncope, palpitations, or both.

1.1. Introduction

This chapter begins by introducing the author before moving on to set the scene and provide the background to the thesis, informing the reader of the clinical problems faced by implantable loop recorder (ILR) patients. The chapter will then briefly cover where and why the REveAL™ - CARElink™ (Real Care) study was carried out. Reveal™ is an implantable loop recorder (ILR) produced by Medtronic Inc., and Carelink™ is the remote monitoring equipment and network used for home monitoring of implantable cardiac devices produced by Medtronic Inc. Real Care was a physician - blinded randomised controlled trial (RCT) which recruited consecutive implantable loop recorder (ILR) patients.

1.2. Professional interest of the author

As a cardiac physiologist working for the National Health Service (NHS) in County Durham and Darlington I am privileged to work with a variety of people of varying ages and walks of life. Whilst all of these people are different they all have something in common; an interest in the heart, diagnosed heart conditions, or potential heart conditions. There are a multitude of different conditions that can affect the heart and various symptoms or problems that

can arise from a heart condition or defect. Whilst I am interested in all cardiology my personal preference is in the fields of cardiac rhythm management (CRM), syncope, and palpitations. It is particularly interesting for me when the diagnostics and management of these fields overlap.

In preparation for undertaking the Real Care study and completing this thesis I attended a variety of courses including MSc level courses on quantitative and qualitative research methods, basic and applied linear regression statistics modules, good clinical practice in research (GCP), and beINFOrMED online consent training and assessment, passed the British Heart Rhythm Society (BHRS) exam, and completed the BHRS professional competency logbook.

1.3. Lay summary of the clinical problem addressed in this thesis

There are many reasons and factors that can cause a person to collapse (syncope or transient loss of consciousness (TLoC)) or suffer from palpitations. Even after extensive testing using wearable external heart monitors or tests designed to stress the body and induce symptoms in a controlled environment, there may be a suspicion but not sufficient evidence that the cause of the problem lies with the heart. In particular the concern is that the patient's symptoms are caused by an abnormal heart rhythm. If a patient's doctor has any suspicions or the symptoms remain unexplained then the doctor may request the use of an implantable heart monitor called a loop recorder.

Implantable loop recorders (ILRs) are small diagnostic devices (approximately the size of a standard USB memory stick) that are implanted just below the

skin and can monitor a patient's heart rhythm and rate by monitoring a single channel of electrocardiogram (ECG) for three years or more. Unfortunately, in some instances diagnosis using ILRs may be prolonged or even come after further injury to the patient or to people around the patient. This could be due to a number of reasons, primarily that the patient may not be seen until after they have had their symptoms or that they may feel that they had not had severe enough symptoms to warrant a check of their device. There are also patients that attend the department that have symptoms that may or may not have resulted in injury due to heart rhythm abnormalities, and on further investigation of the device we find that this could have been prevented. The reason for this is that the patient may have had heart rhythm abnormalities which required intervention but were unaware of them at that time and the ILR's auto detection function had recorded.

New technology means that patients can send their ILR recordings from home and be checked more regularly by their follow-up physiologists and their physicians where necessary.

This thesis aims to give an account of the different types of syncope and palpitations, leading on to explore the evidence behind the use of ILRs in the diagnosis of these conditions. Once the rationale and methodology of the Real Care study has been provided, the thesis will examine the data collected from the Real Care study to establish whether the new equipment is a feasible option to improve patient care and reduce the time taken to confirm or exclude cardiac involvement as a cause for patient's symptoms.

1.4. Incidence data on syncope in the UK

The annual incidence of patients presenting with syncope in a UK setting has been estimated at approximately 2.7 per 1000 population (1). With a population of just over 605,000 (2) in the County Durham and Darlington area, that would imply that around 1,634 patients within the County Durham and Darlington NHS Foundation Trust (CDDFT) catchment area will have a syncopal episode each year. It is further suggested that 259 (16%) (1) of these patients will have an arrhythmic cause for their syncope. While these are estimated figures on the incidence of syncope it is also reported that due to misdiagnosis of epilepsy and other causes of TLoC the true incidence could be 20-30% higher (3,4). In a costing statement carried out by the National Institute for Health and Clinical Excellence (NICE) (4) it was reported that estimating the number of patients that require an ILR is not possible for the same reasons, as any numbers could potentially be an underestimation.

1.5. Conventional care in the management of syncope

Conventional care in the management of syncope varies greatly; within the UK there is a choice of either the National Institute of Health and Clinical Excellence (NICE) or the European Society of Cardiology (ESC) guidelines (4,5). Whilst there is a move towards the use of the guidelines within cardiology and among those with a specialist interest in falls and syncope, there are still a large number of patients that are misdiagnosed or not referred for specialist assessment (3,4). This may be as a result of there being no clear pathway both within the acute setting and within the wider community setting (1). Therefore at the current time it is difficult to completely adopt any single set of guidelines and eliminate historical practice, but with that said, the

use of referral pathways is increasing within the falls and syncope setting throughout County Durham and Darlington NHS Foundation Trust (CDDFT) hospitals.

In the CDDFT setting, falls and syncope are generally referred to and assessed by cardiologists or elderly care consultants with a specialist interest in syncope and the support of cardiac physiologists with specialisms in either echocardiography (echo) or cardiac rhythm management (CRM), and a specialist interest in syncope. With more patients being referred to these specialists and the proposed introduction of a dedicated and structured Falls and Syncope Service within CDDFT hospitals, the shift towards following the pathways suggested by ESC and NICE has increased the use of diagnostic tools such as the ILR which is the main focus of this thesis. More specifically the way in which ILR patients are followed up and managed.

1.6. Conventional care and follow-up of CDDFT ILR patients

When a patient has an ILR implanted they are routinely followed-up at five-weeks and then every six-months. The patient may be seen more regularly if they have their symptoms or if the physiologist feels that more frequent follow-up is required, but in general patients are only seen at six month intervals.

1.7. Proposed care and follow-up of CDDFT ILR patients

It is now possible for ILR patients to have an additional piece of equipment to use in conjunction with their ILR which enables them to send information recorded automatically by, or manually on their device via phone to their CDDFT physiologists. This equipment means that follow-ups can be carried

out more frequently without the need for patients to attend their follow-up department at the hospital. It is proposed that using the home monitoring equipment, patients should be followed-up remotely at fortnightly intervals and additionally if symptoms occur.

1.8. Primary and secondary research questions

The primary research question for this thesis is:

'Can patients with implantable loop recorders have true event ECGs followed-up sooner and can they receive a cardiac or non-cardiac diagnosis for their symptoms in a shorter average time if remote monitoring is employed into their care pathway?'

The secondary research questions for this thesis are:

1. How much data is generated for review (review burden) by true and false recordings, both with and without the use of remote monitoring?

2. Does remote monitoring impact ILR memory saturation?

3. Can age or gender be used as determinants to predict diagnosis?

4. What CDDFT's ILR diagnostic yield is.

5. What is the trigger for true and false ILR recordings in terms of arrhythmia, artefacts or signal sensing and how do they breakdown into diagnosis?

6. How long does it take to record the first true event?

7. What the primary implant indications are in CDDFT hospitals.

8. What is the response to diagnosis (in terms of monitoring).

The primary and secondary research questions are covered in more detail in Chapter 3. Real Care study aims, objectives, design and implementation.

Chapter 2. A review of the literature

This chapter is split into two distinct modules, the first module (sections 2.1 - 2.6) is not technically a literature review, rather it is a hybrid of clinical knowledge and supporting literature evidence. The second module (sections 2.7 - 2.10) follows the traditional approach and critically appraises the limited data available on implantable loop recorders (ILRs) in conjunction with remote monitoring. Whilst unconventional, the approach is important to give the reader an understanding of the scope of the problem when diagnosing syncope and palpitations, the variety of tests used to reach a diagnosis, and highlight why minimising diagnostic time is important. Once the underpinning knowledge and the common tests for syncope and palpitations have been covered the chapter will move onto the history of ILRs and the technological advances that have led to the availability of remote monitoring (including how remote monitoring has proved a valuable tool for other implantable cardiac devices). In the second module the publications that were reviewed and appraised in order to make the REvEAL™ and CARElink™ (Real Care) study bridge the gap in the evidence by being as robust as possible will be presented. Finally in sections 2.11 and 2.12 the literature review will be summarised.

Due to the way in which the chapter is presented the resources explored will be presented in section 2.1 but the detailed search strategy for evidence relating to ILR in conjunction with remote monitoring will be given in section 2.6.

2.1. Resources explored

The evidence searches (Module 1) literature review (Module 2) were carried out using information gained from various sources. The search terms used were ultimately chosen by the author but discussions that led to the choosing were held with Professor Murphy and Jane Curry. The main search sites used to locate the literature were PubMed, Medline, Ovid, Allied and Complementary Medicine (AMED), Excerpta Medica Database (EMBASE), Health Management Information Consortium (HMIC), British Nursing Index (BNI), PsycInfo, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Health Business Elite. However Google and Google Scholar were also used to locate key articles and information. Following the search an NHS Athens account, the CDDFT library, or the Durham University library was used to obtain the relevant articles and literature from a credible source such as a peer-reviewed journal or book.

2.2. Syncope and palpitations

Syncope originates from the Greek word Λιποθυμία, **συγκοπή** or sunkopè meaning to interrupt or cut off (6,7). In medical terms syncope means transient (short-lived or temporary) global hypoperfusion of the cerebral cortex (lack of blood to the brain) which may be related to a drop in blood pressure or an abnormality of the heart's rate and / or rhythm (4,5). The term is used when the hypoperfusion of the brain causes loss of consciousness and postural tone. Syncope is often referred to as transient loss of consciousness (TLoC) or 'blackouts'. There are fairly distinct characteristics of syncope, these are:

1. Rapid onset

2. Short duration

3. Spontaneous complete recovery

There are four main groups into which syncope is classified with each of these being subdivided further (5):

1. Neurally Mediated

2. Orthostatic (postural) Hypotension

3. Cardiac Arrhythmias

4. Structural e.g. aortic stenosis or hypertrophic cardiomyopathy (HOCM)

Neurally mediated syncope (NMS) has several commonly-used terminologies such as vasovagal or neurocardiogenic, all three of these names allude to the same thing, syncope caused by a decrease in blood pressure and a drop in heart rate that is caused by an abnormal response from the autonomic nervous system (8). Under normal circumstances the blood pressure is constantly changing and being regulated by various complex reflex mechanisms (9). If the blood pressure was to drop due to venous pooling, for example as result of a prolonged period of standing then this would be sensed by the baroreceptors (pressure sensors) in the aortic arch and carotid sinuses

(10). On sensing the drop in blood pressure the correct response would be for the drive from the sympathetic nervous system to be increased causing an increase in heart rate, vasoconstriction, and reducing blood flow to non-vital organs to increase peripheral resistance. Once the blood pressure is back to normal the sympathetic drive is reduced and the heart rate, vasculature, and blood flow to organs relax back to a normal state. In most cases these changes are carried out in a short time frame and are therefore barely perceptible (11).

If the system fails and an abnormal autonomic response occurs it is thought to be caused by a sequence of events:

1. Partial emptying of the heart caused by reduced venous return due to the shift of fluid into the lower extremities.

2. Hypercontractility of the ventricles as part of the normal sympathetic response as the system attempts to increase cardiac output.

3. The mechanoreceptors (stretch receptors) in the heart are paradoxically stimulated as a result of the under-filled heart being hypercontractile.

4. The abnormal impulses from the stretch receptors are transmitted to the tractus nucleus solitarius which initiates the parasympathetic (vagal) drive and inhibits the sympathetic drive.

5. This results in bradycardia, increased hypotension, and syncope.

While this is the traditionally accepted pathway for NMS (12), evidence suggests that there are various other contributory factors such as neurohormonal sympathetic inhibition or the possibility that carotid and aortic baroreceptor function on the sympathetic nervous pathways is impaired in patients predisposed to NMS (13).

Orthostatic Hypotension (OH) is essentially the same as NMS, however it has specific criteria for diagnosis and can, if asymptomatic, precipitate a NMS attack (14). The diagnostic criteria recommended in Europe by the European Federation of Neurological Societies (EFNS) are a systolic BP drop of ≥20mmHg or a diastolic BP drop of ≥10mmHg, within 3 minutes of posture change from supine / sitting-to-erect (15).

The final two forms of syncope, viz; cardiac and structural, do to a large extent cross over but in general terms cardiac syncope refers to isolated electrical abnormalities of the heart that cause a fast rhythm (tachycardia) or a slow rhythm (bradycardia). Both could have ischaemic or non-ischaemic causes (16). In the strictest of terms a bradycardia is considered to be a heart rate below 60 beats per minute (bpm) (17), in practice however a bradycardia is not considered to be significant unless the heart rate falls below 40bpm during symptoms (16).

There are several types of bradycardia though they tend to come under two main headings (18,19):

1. Sick Sinus Syndrome (SSS) also commonly referred to as sinus node dysfunction (SND)

(i.) Sinus bradycardia – The heart rate is below 60bpm but the conduction of impulses through the heart are following the normal pathways.

(ii.) Sinus arrest – This is when the sinoatrial (SA) node fails to depolarise, the time that the node is in an arrested state can vary from one beat to 30 seconds or more.

(iii.) SA exit block – This is when the cells of the sinus node fails to conduct to the surrounding atrial tissue, this block could be of the first degree meaning that its conduction is delayed, second degree meaning that every other impulse is blocked or third degree meaning that every impulse is blocked.

2. Atrioventricular (AV) conduction defects

(i.) First degree AV block – The conduction between the atria and the ventricles is delayed for longer than the normal time of 120-200ms.

(ii.) Mobitz I second degree AV block – the time taken for conduction between the atria and ventricles prolongs with each beat until the atrial impulse is blocked at the AV node.

(iii.) Mobitz II second degree AV block – 2:1, every other atrial impulse is blocked at the AV node.

(iv.) Third degree AV block or complete heart block – There is no conduction through the AV node and the heart is reliant on an escape rhythm (a rhythm initiating from a different focus in the heart) for depolarisation.

While all of the above defects have been described in terms of conduction through the atria and ventricles it may be prudent to mention that conduction of the heart is often described in terms of the depolarisation and repolarisation of the atria and ventricles as seen on the surface ECG. In nearly all cases the Q from PQRST is dropped as there is not always a Q wave present and measurements of AV conduction are described as PR interval.

All heart rates above 100bpm are considered to be a tachycardia. However not all tachycardias are abnormal and the heart rate may have increased as a normal physiologic response due to exercise or stress which makes the onset of a tachycardia an important factor as most tachycardias with gradual onset are physiological and therefore not problematic. Tachycardias with sudden onset in most cases are non-physiological. The origin of tachycardias is generally speaking from the atria or the ventricles, supraventricular or ventricular respectively. While supraventricular tachycardias are rarely life threatening in adults they can make patients feel particularly unwell, with symptoms including but not limited to; shortness of breath, dizziness or syncope, and on occasion patients also report simply having a sinking feeling in their chest or stomach. Tachycardias with ventricular origins such as ventricular tachycardia (VT) and ventricular fibrillation (VF) are more

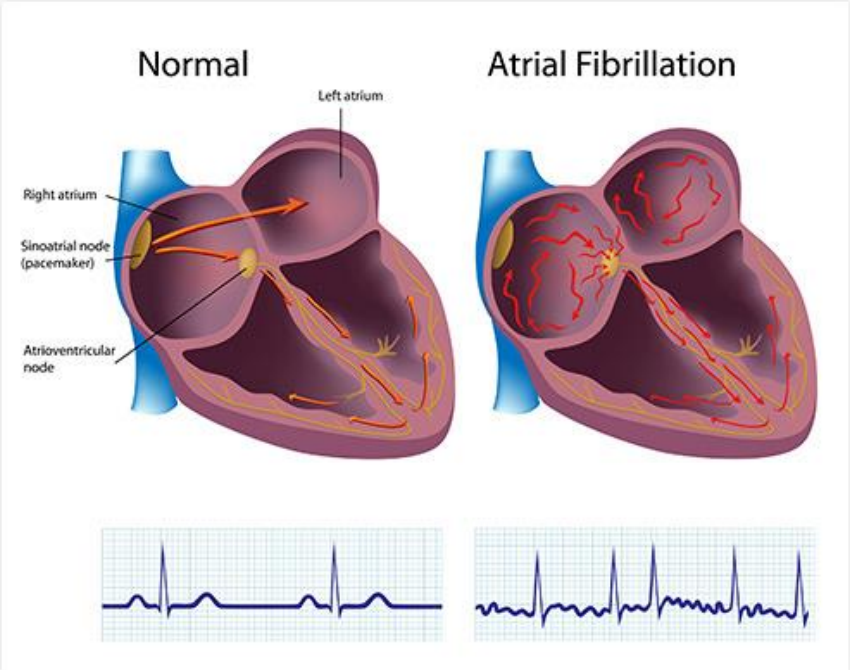
commonly related to haemodynamic compromise and become fatal if untreated.

Palpitations are defined as an awareness of the heartbeat, this can be in the form of a fast, irregular, hard or missed beat or beats. Palpitations are often described by patients to be felt in the chest, neck, throat or stomach (20).
As previously mentioned tachycardias commonly come under the categories of atrial or ventricular however there can also be tachycardias originating from the junction between the atria and the ventricles, these are simply referred to as junctional tachycardias.

In the category of atrial tachycardias there is:

1. Atrial fibrillation (AF) – In AF evidence suggests (21) that impulses initiating in the pulmonary veins cause the cells in the atria to fire at random in a disorganised and irregular fashion. The disorganised impulses are then conducted through the AV node at random giving rise to the term irregularly irregular rhythm. As the term irregularly irregular rhythm implies, there is no pattern in the conduction through the AV node. On the surface ECG AF appears as a completely random array of QRS complexes with an erratic baseline. If the AV node is intact then ventricular rates of patients in AF can be up to or in excess of 200bpm. In Figure 1 - The electrical pathway for normal sinus rhythm and AF can be seen.

Figure 1 - The electrical pathway for normal sinus rhythm and AF



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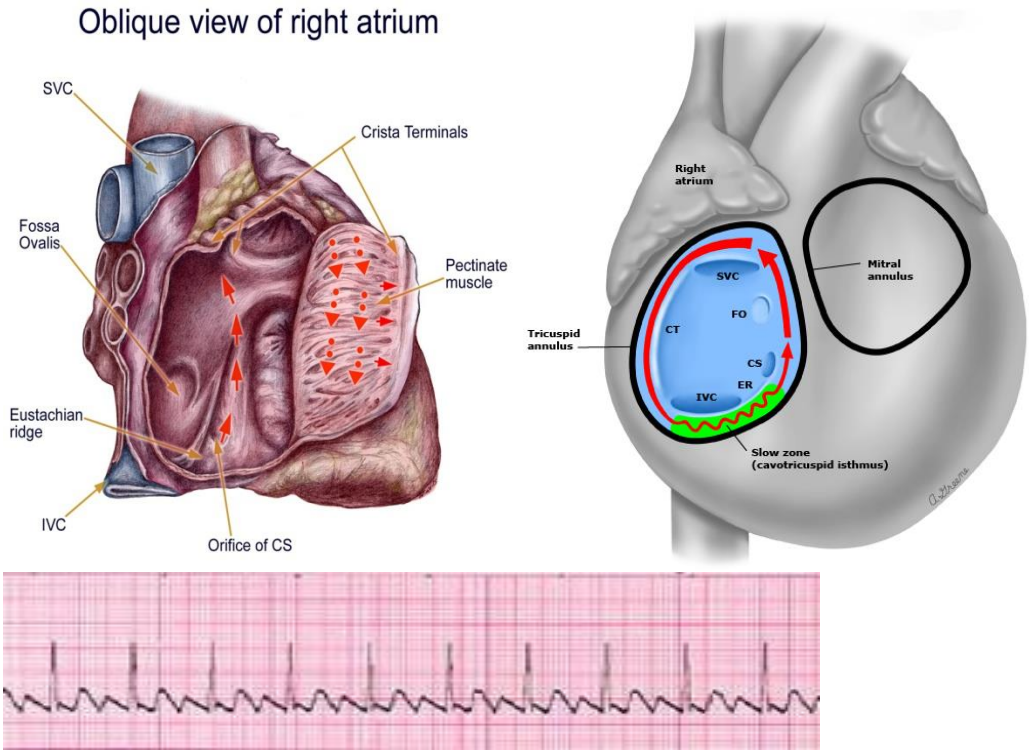
Atrial Flutter – There are several types of atrial flutter which are classified as typical or atypical. For the purpose of this explanation the focus will be on typical atrial flutter. The atrial rate in atrial flutter is commonly 300bpm but can vary between 200 – 350bpm, the ventricular rate is governed by the AV node. In the majority of cases there is some degree of AV block, this is normally 2:1 or 3:1, giving ventricular rates of 100-150bpm. The impulse travels through the right atrium along a well-defined pattern or macro re-entrant pathway around the tricuspid annulus. The circuit in atrial flutter is made stable by anatomical blockades formed by the vena cava, the crista terminalis and the coronary sinus.

Figure 2 - Anatomical structures creating the atrial flutter pathway



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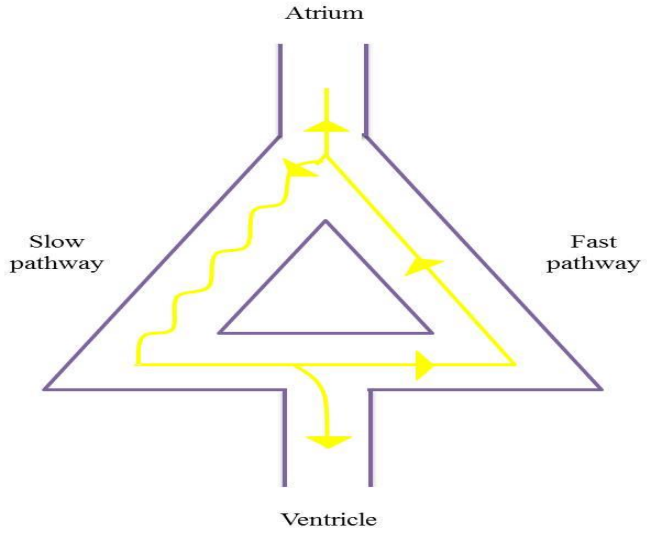
2. AV Nodal Re-entrant Tachycardia (AVNRT) – For AVNRT to exist there has to be a fast pathway and a slow pathway. The exact mechanism is still not fully understood but electrophysiological (EP) studies have significantly improved understanding and led to the widely accepted explanation (22). From EP evidence and historical models, the impulse pathways of AVNRT go around or through the AV node (23). The most common type of AVNRT uses the slow-fast route meaning that the impulse travels down the slow pathway and initiates the ventricular contraction but a portion of the impulse continues to travel back up the fast pathway as the impulse comes back up the fast pathway it initiates depolarisation of the surrounding atrial cells which in turn blocks the intrinsic P wave and the impulse continues back down the slow pathway.

Figure 3 - Schematic representation of the AVNRT electrical pathway shows the theory behind the slow-fast AVNRT.

Figure 3 - Schematic representation of the AVNRT electrical pathway



3. AV Re-entrant Tachycardia (AVRT) – AVRT pathways operate on a similar principle to AVNRT except that the re-entrant pathways are classified as macro circuits and that they cross the electrically inert fibrous divide between the atria and the ventricles *via* an accessory pathway. Accessory pathways in most forms of AVRT conduct in the retrograde meaning that the signal travels from the ventricles to the atria and are blocked in the anterograde (atria to ventricles) direction. AVRT is initiated by an atrial premature beat, the accessory pathway is refractory when the impulse reaches it so the only conduction to the ventricles is through the AV node. By the time the impulse has travelled through the ventricles the accessory pathway is recovered and the impulse re-enters the atria and the tachycardia begins. This type of tachycardia normally has a narrow complex (this usually refers to a QRS measurement on the surface ECG

of 80 – 120ms) unless there is a pre-existing or a functional bundle branch block (BBB). P waves in AVRT are sometimes visible as a notch in the QRS or just after the QRS in the early ST segment and will be on a 1:1 basis. The rate of an AVRT is usually between 120 and 250bpm. In true AVRT the 1:1 conduction will not be affected by drugs or manoeuvres such as the Valsalva, which affect AV conduction speed. If the ventricular rate but not the atrial rate is affected then it is more likely to be an atrial tachycardia or atrial flutter.

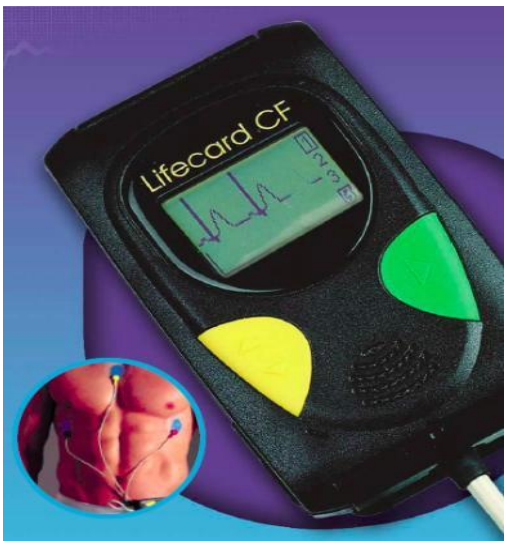
2.3. Common tests used for syncope and palpitation diagnosis

There are a few tests that are commonly used in diagnosing or attempting to diagnose both syncope and palpitations that occur infrequently, but the use of these tests are not always the most appropriate or cost effective (3,5,14,24). The terms infrequent and infrequently refer to symptoms that occur less than fortnightly. While the use of the following tests are common there have been pathways developed and tested over recent years which suggest that with a thorough history and basic cardiovascular assessment then the tests need not be done. If there is still doubt surrounding the origin of the problem then an ILR should be implanted (1,3,5,16). However it is important to cover the tests here as they are still widely used in clinical practice.

Possibly the most common test for infrequent syncope or palpitations is the 24 hour - seven day Holter monitor or ambulatory ECG recording device. The devices are named Holter monitors after the creator Norman Holter who first invented the device in the 1950s and introduced it into clinical use in the 1960s (25,26). A Holter monitor is capable of recording several channels of

continuous ECG, often two or three channels depending on the duration of recording. The monitors can record for up to seven days with a single battery and memory card. The device is attached to the patient for the selected amount of time using adhesive electrodes. The patient is then free to carry out their normal day-to-day activities providing that they do not submerse the device in water, i.e. no baths, showers, or swimming etc. Figure 4 shows a Spacelabs Healthcare Lifecard CF® digital Holter monitor.

Figure 4 - Spacelabs Healthcare Lifecard CF® digital Holter monitor



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Once the device is returned the recording is analysed. The analysis is carried out using specialist software by physiologists or specially trained healthcare professionals and a factual report is produced. Whilst the Holter monitor is a valuable tool it is not without its flaws. If the appropriate skin preparation is not carried out or the stickers become dry then the recording can be very artefactual which can in extreme cases render the recording unusable. Other problems that can occur are the disconnection of leads whether accidental or

deliberate, or in some cases the device is actually dismantled. There is also the problem of symptoms not occurring while the monitor is attached. In some instances the test is repeated multiple times with no diagnostic value.

The next diagnostic tests to be covered are the external loop and cardiac event recorders. Like Holter monitors there are several makes and designs of external loop recorder and cardiac event recorder. The principle is similar for both with the only differences being;

1. The duration of recordings and the capacity of the device.

2. The way in which recordings are made.

The first of these points is relatively self-explanatory but the second may require some explanation. In the case of cardiac event recorders the devices record a rhythm strip of one to two channels of ECG. The duration of these strips varies from manufacturer to manufacturer and in many cases is programmable. The method of recording can also vary, there are devices which attach in the same way as a Holter monitor and there are those that have metal studs on the outer casing that is held against the chest during a symptom episode. In both cases however cardiac event recorders only record if activated externally. External loop recorders are attached to the patient using adhesive electrodes and incorporate all of the features of the cardiac event recorder but also monitor on a continuous loop. This means that they can record variations in heart rhythm and rate without the need for outside activation (27). Most modern external loop recorders and cardiac event

recorders are capable of recording for up to one month on each set of batteries. Unfortunately many patients suffer reactions to the adhesive electrodes after just a few days. Whilst every effort is made to prevent this by repositioning stickers and removing devices for baths and showers, the devices can become uncomfortable and even begin to interfere with people's lives during prolonged monitoring. Figures 5 and 6 show a Reynolds Medical (now Spacelabs Healthcare) Cardio Call and a Novacor Rtest respectively. The Cardio Call can be used as either a monitor that has the metal studs placed against the skin during a symptom episode, or as a wired monitor but will only record if activated externally. The Rtest has the ability to record strips on external activation but will also record rhythm strips if programmable parameters are met.

Figure 5 - Spacelabs Cardio Call cardiac event recorder

(Permission requested from Spacelabs Healthcare UK September 2016)

Figure 6 - Novacor Rtest external loop recorder

(Permission requested from Novacor UK Ltd. September 2016)

The last diagnostic test to be covered is the head up tilt (HUT) test. The HUT was the result of several studies carried out in the 1800s, these studies culminated with the work of Hill (1895). While others had used positional changes in their work, Hill was the first to use a table and outstretched limbs (28). The research around syncope continued into the early 1900s but the next milestone for the HUT was not until 1957 when researchers used university students tilted to 60˚ with or without the use of sodium nitride to induce syncope (29). HUT as a diagnostic tool for unexplained syncope was not reported to be clinically useful until the mid 1980s, some 90 years after its inception (30). By the early 1990s HUT was widely accepted as a clinically useful tool but due to the variety of techniques giving a variety of sensitivity and specificity results the American College of Cardiology (ACC) was prompted to review the evidence and produce one of the first expert consensus documents on HUT (31).

The principal of the HUT is simple, and while predominantly aimed at NMS it is also effective in patients with other forms of reflex syncope and patients with sick sinus syndrome (SSS) (32). The attraction to the use of HUT is that symptoms can be reproduced in a safe and controlled environment. If patients are held at an angle of between 60 – 70˚ then venous pooling will occur and venous return will reduce as a result of the orthostatic stress and immobilisation. If the test is positive meaning that symptoms are reproduced, then following the period of stress, hypotension and a drop in heart rate will occur due to impaired vasoconstrictor capability, withdrawal of sympathetic nervous stimulation and hyperactivity of the vagal tone (33). HUT in general can be classified as provoked or unprovoked. There is also lower body negative pressure (LBNP), essentially LNBP induces the same physiologic response as HUT. However the venous pooling in the vasculature of the pelvis and legs is induced by applying sub atmospheric pressure around the lower body (34). Provocation can be carried out using several pharmaceutical methods, Isoproterenol and nitroglycerine are the most common drugs used (5).

There are two main protocols used for HUT; the Italian protocol and the Newcastle protocol (4,5,35,36). However in the 2008 Newcastle protocol update there was a consensus between the two protocols (33). In the CDDFT HUT service we use a hybrid of the Newcastle protocols (33,36) and the orthostatic hypotension (OH) framework (37), incorporating the active stand and the HUT.

Patients are asked to fast for four to six hours prior to the test. On arrival to the department they are taken in to the test room, the test is fully explained and the history of their symptoms is taken again. Once the patient is happy and has given consent to proceed they are attached to the monitoring equipment and strapped to the tilt table in the supine position. Once the patient has rested for approximately 15 minutes and the equipment has been validated (the process of ensuring that the beat to beat and oscilometric blood pressure are correlated) the patient is angled to 90° for two minutes. After two minutes the patient is returned to the supine position for a further two minute rest period. The next stage is the HUT, the patient is tilted to the 70° position where they remain for 20 minutes. If the test has not achieved a positive result after the initial 20 minutes at 70° then providing there are no contra-indications they are given 400µg of glyceryltrinitrate (GTN) sublingually. The patient will then remain at 70° for a further 15 minutes. If there are contra-indications to GTN then an unprovoked HUT will be carried out. In the unprovoked HUT patients remain at 70° for 40 minutes. In both cases the 'healthy' patient should be able to maintain blood pressure and consciousness.

Whichever test is carried out, the test is ended if the patient suffers a symptomatic episode, feels unable to continue with the test, or the test reaches its endpoint. In patients over 50 years of age there is another element to the test. Providing there are no contra-indications and the patient gives consent then left and right carotid sinus massage (CSM) will be carried out in the supine and erect positions with two minute intervals between each massage. CSM is a test designed to assess the presence of carotid sinus

syndrome (or hypersensitivity). By massaging the carotid sinus for between five and ten seconds the pressure caused by the massage mimics an increase in blood pressure, the resultant autonomic response causes a transient increase in vagal tone (reducing heart rate) and reduction in peripheral vascular resistance due to dilation of the blood vessels. The key word here is transient. In individuals with carotid sinus hypersensitivity, the effect is still considered transient but is markedly more significant. In situations where carotid sinus hypersensitivity is present the response to CSM can produce significant bradycardia / asystole (cardio inhibition), marked hypotension (vasodepression), or both (38).

Figure 7 - HUT table and monitoring system

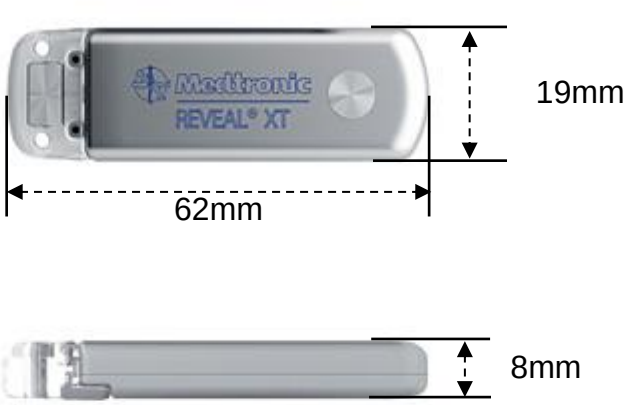
(Permission requested from CNSystems Austria May 2017)

2.4. Implantable loop recorders.

The implantable loop recorder (ILR) whilst not considered an uncommon test, it is considered to be an underutilised tool in the diagnosis of syncope and palpitations (3,5,4,39,40). As ILRs are the main focus of this thesis they are covered separately in this section and not included in 2.3.

ILRs are small diagnostic devices that are capable of recording a single channel of electrocardiograph (ECG) over an extended period of time (3). The current mainstream devices Medtronic Inc.'s Reveal™ DX and XT shown in Figure 8 are comparable in size to a USB memory stick measuring 62 x 19 x 8mm with a volume of 9cc and a weight of 15g. The main casing of the Reveal™ is constructed using titanium with a polyurethane and silicone header. The whole construction with the exception of the two 43mm^2 (surface area) electrodes is then hermetically sealed and encased in parylene. The effective distance between the electrodes is 40mm. Reveal™ devices are powered by a 3.6 volt lithium thionyl chloride battery with a projected longevity of three years (41).

Figure 8 - Reveal™ XT and DX Dimensions



The ILR device is implanted using local anaesthetic in the subcutaneous tissue of the left hemithorax (42). The indications for the use of ILRs include, but are not limited to, the diagnosis of unexplained syncope or transient loss of consciousness (TLoC) where cardiac involvement such as an arrhythmia is suspected or indicated but not confirmed (43), palpitations, and observation-

guided management of atrial fibrillation (AF) patients (3). In many cases the use of ILRs comes after the repeated use of tests described earlier in this chapter such as Holter monitoring, external loop recorders or HUT; however in some cases, the European Society of Cardiology (ESC) and The National Institute for Health and Clinical Excellence (NICE) suggest early use of ILRs for symptoms considered to be infrequent (less than once every two weeks). Both NICE and the ESC state that after initial assessment and subsequent cardiovascular assessment by a suitable person or physician, if TLoC/syncope occurs infrequently and is believed to be due to cardiac arrhythmia, or remains unexplained then an ILR should be employed (4,5). Results from the place of Reveal™ in the care pathway and treatment of patients with unexplained recurrent syncope (PICTURE) study demonstrated a high diagnostic yield from ILRs and suggested that the devices were under-utilised in clinical settings and that better adherence to guidelines could reduce the wasted tests and consultations that many patients go through (40). It has also been suggested that if ILRs are used as laid out in the guidelines produced by NICE (4) in the UK, they are cost effective (39). While ILRs are considered an effective tool the recorders suffer from memory saturation, meaning that events are logged but not available for analysis, this is in part due to over-sensing and under-sensing (43). The current method of in-office follow-up promotes saturation and potentially prolongs diagnosis and/or treatment (44,45).

Delaying treatment can have an impact for the patient in several ways. In terms of driving a ban of four weeks extending indefinitely until the cause is identified can be imposed. The reason for the stringency is that syncope is

two to three times more likely to cause a road traffic collision than epilepsy (46). There is also evidence that prolonging diagnosis can lead to further symptoms and hospitalisations (47) and anecdotally patients report impacts upon their quality of life, stating that they do not want to leave their house or that they cannot go and do day to day activities for fear of symptom recurrence.

2.5. The history and technical advances of implantable loop recorders

In County Durham and Darlington NHS Foundation Trust (CDDFT) hospitals only Medtronic Inc.'s Reveal™ ILRs are currently implanted. For this reason the focus of this history was on those devices but competitors' devices were not overlooked and will be mentioned herein. Anecdotally the Reveal™ family of ILRs has dominated the ILR market, and while other manufacturers have tried to compete such as St Jude Medical with their Confirm™ device and Biotronik's BioMonitor™ it appears unlikely that this dominance over the market will be threatened any time soon, certainly within the North East of England.

The first published report of ILRs being used in clinical practice was published in the late nineties by Krahn et al. (48), the research for their paper involved ILRs that were implanted between 1992 and 1994. The ILRs used in the studies of the early nineties were manufactured by Medtronic Inc. and were comparable in size to a single chamber pacemaker (48), much larger than the Reveal™ ILR devices that were launched in 1998 also by Medtronic Inc. The original device had longevity of 14 months and only recorded when activated.

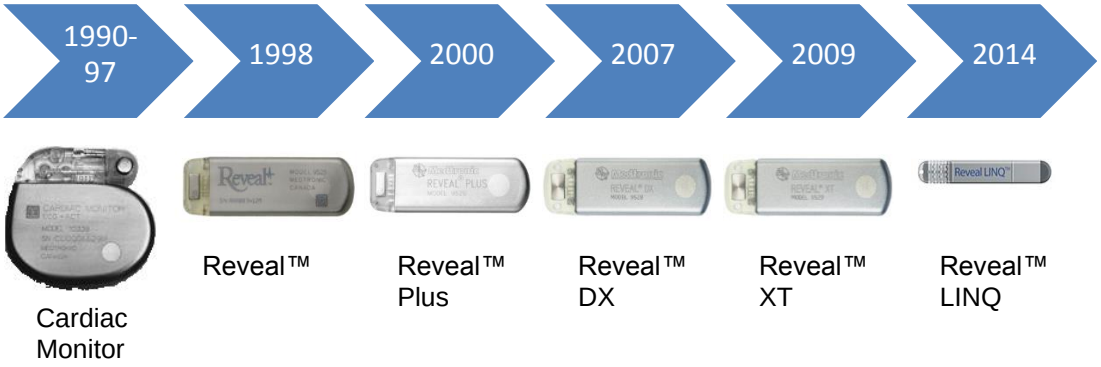
The Reveal™ was replaced in 2000 by the Reveal™ Plus. Both the Reveal™ and the Reveal™ Plus devices were capable of recording 42 minutes of single lead ECG and the introduction of the Reveal™ Plus maintained the 14 month longevity. However, the Reveal™ Plus had the additional feature of automated recording. This feature was a huge step forward for these devices as it meant that even if the manual activator was not used during a symptomatic episode or if patients were non-compliant with the activator but an arrhythmia was present then there was still a chance that the information would be collected (49). As with all new advances in technology, the automatic recording function was not welcomed by everyone. Some felt that the automated recordings did not improve a patient's diagnostic journey and that it increased the clinical workload with analysing false recordings or recordings containing artefacts (50,51).

The next device in the Reveal™ family, the Reveal™ DX was not introduced until 2007. The DX brought with it several improvements; sensing and detection enhancements which reduced false and artefactual recordings, improved longevity of up to 36 months and larger recording capacity of 49.5 minutes. As with all ILRs the device memory could be overwritten if the patient used the manual activator after or during a symptom, or erased by the physiologist during follow-up so that the device is ready to record anew (52).

In 2009 the Reveal™ XT was launched. This introduced the AF detection algorithm and the cardiac compass which gives the clinical team more information such as heart rate and AF trend data on a rolling 14 month window.

Both the Reveal™ DX and XT are still available and in February 2014 the Reveal™ LINQ was added to the Reveal™ family tree. The LINQ is smaller than all of its predecessors by 87% and has enhanced capabilities such as wireless transmission and larger memory, of up to 57 minutes: all whilst maintaining the three year longevity (53). Unfortunately the Reveal™ LINQ is not yet in mainstream use. In our Trust this is in part down to the relatively high cost. Currently the LINQ is more than double the price of the XT. The overall progression of Medtronic Inc. ILRs can be seen in Figure 9 - Timeline of Medtronic™ Reveal™ device family

Figure 9 - Timeline of Medtronic™ Reveal™ device family



The Reveal™ DX and XT ILRs are capable of storing 49.5 minutes of recording which is broken down into three, seven and a half minute manually activated recordings and 27 one minute automated recordings. It is worth noting at this point that the configuration of the manually activated recordings can be altered to record two, ten minute recordings or one, 15 minute recording. Manual recordings collect ECG for a period of time both before the ILR was activated and after. In all cases the majority of the recording is collected retrospectively, either six and a half minutes, nine minutes or 14

minutes depending upon the manual recording option chosen. In all cases of manual recording one minute of recording will be stored post activation.

The automated recordings are stored as one of four or five categories (dependent upon device, i.e. DX or XT);

1. Fast ventricular tachycardia (FVT)

2. Ventricular tachycardia (VT)

3. Bradycardia (Brady)

4. Asystole

5. Atrial tachycardia / Atrial fibrillation (AT / AF) (not available on the DX model)

The automated storage parameters are adjustable allowing the device to be tailored for the patient's or the clinician's requirements. An example of this tailoring would be reducing the rate at which the device determines a FVT or a VT or reducing the number of beats required before a device can classify a rhythm. The typical CDDFT Reveal™ XT device parameters are shown in Table 1 - CDDFT ILR implant typical settings, a Reveal™ DX would be setup in the same way without the AT/AF setting as it is not available on the DX.

Table 1 - CDDFT ILR implant typical settings

	Detection Rate (bpm / ms)	Detection Duration
FVT	176 / 340	12 / 16 beats
VT	150 / 400	12 beats
Bradycardia	40 / 1500	4 beats
Asystole	-	3 sec
AT / AF	-	>6 mins

The detection rate column in the table refers to the heart rate in beats per minute or R-R interval in milliseconds before the device can classify an auto recording. The detection duration is the number of beats or in the case of asystole the duration required at the detection rate in order for the device to record an automated recording.

In addition to the settings in Table 1 there are several other settings that are routinely switched on either prior to implant during the device set – up or shortly after device activation, ectopy reject is turned on and the detection enhancement settings are turned on to their default values.

It is worth mentioning the follow-up procedure at this point, however it is only covered lightly as the process concerning significant recordings is covered in more detail in section 3.14 Procedure for all follow-ups with significant ECGs on page 84. At all CCDFT ILR follow-up appointments patients are asked how they have been and if they have had any symptoms, the device is then interrogated and recordings are reviewed. Once the appropriate printouts of ECGs, ECG logs, and heart rate trend information has been printed and saved the device memory is wiped so that the device is ready to start collecting data again.

2.6. Remote monitoring

A recent advance in ILRs has made the use of remote monitoring available as an alternative or as a supplement to in-office follow up. There is readily available research on the effective use of remote monitoring with other implantable cardiac devices such as implantable cardioverter defibrillators (ICDs), cardiac resynchronisation therapy (CRT) devices and pacemakers (PMs) (54,55,56,57,58). A study by Raatikainen and colleagues (57) found that remote monitoring in the ICD patient population was a safe and cost-effective alternative to in office follow-up. Other studies found that in patients with ICD and CRT devices, not only can remote monitoring improve the management of arrhythmias but it can also reduce heart failure hospitalisations, appropriate and inappropriate ICD shocks, and potentially reduce mortality (54,59,60). Furthermore it has been shown that using the data recorded on pacemakers (particularly relating to atrial arrhythmias, remote monitoring can reduce stroke occurrence and hospitalisations (60). One of the pivotal moments for remote ICD monitoring that led to it being considered valuable for patients and clinical staff was the recommendation by the US Food and Drug Administration (FDA) that remote monitoring is a valid safety tool (61,62). The recommendation was due to problems with ICD lead systems such as St Jude's Riata family of leads or Medtronic's Sprint Fidelis lead. The lead problems were different for both manufacturers, for St Jude the problem was insulation failure (62) and for Medtronic it was lead fracture (61). However both had the same potentially serious risks attached the most serious risk was death, caused by failure of the device to deliver therapy. Other issues related to these lead problems were inappropriate shocks which are associated with not only increased mortality but also psychological

implications (i.e. depression and anxiety), and abnormal sensing and pacing (59,60,61,62,63). Furthermore, the latest Heart Rhythm Society guidelines for pacemakers, ICDs, and CRTs now stipulate that the devices should be routinely monitored via remote systems and that the equipment is best prescribed within two weeks of implant (64).

Remote monitoring has been trialled in other areas of medicine, in diabetes for example as a viable form of controlling blood glucose and activity for patients with type two diabetes (65), and for preventing nocturnal hypoglycaemic and hyperglycaemic events in children with type one diabetes (66) but the evidence suggested that further research and development was required to improve compliance and efficacy. Recently a closed loop system that automatically adjusts insulin via a smartphone app which also transmits data to clinicians or caregivers was trialled with promising results but again further research is required (67).

Due to the infancy of remote monitoring in ILRs there is still very limited data available (44), which will lead us on to the focus of this literature review. However it is first necessary to provide an understanding of the way in which remote monitoring works. The example used will be the Medtronic Inc. version of remote monitoring the Carelink™ network.

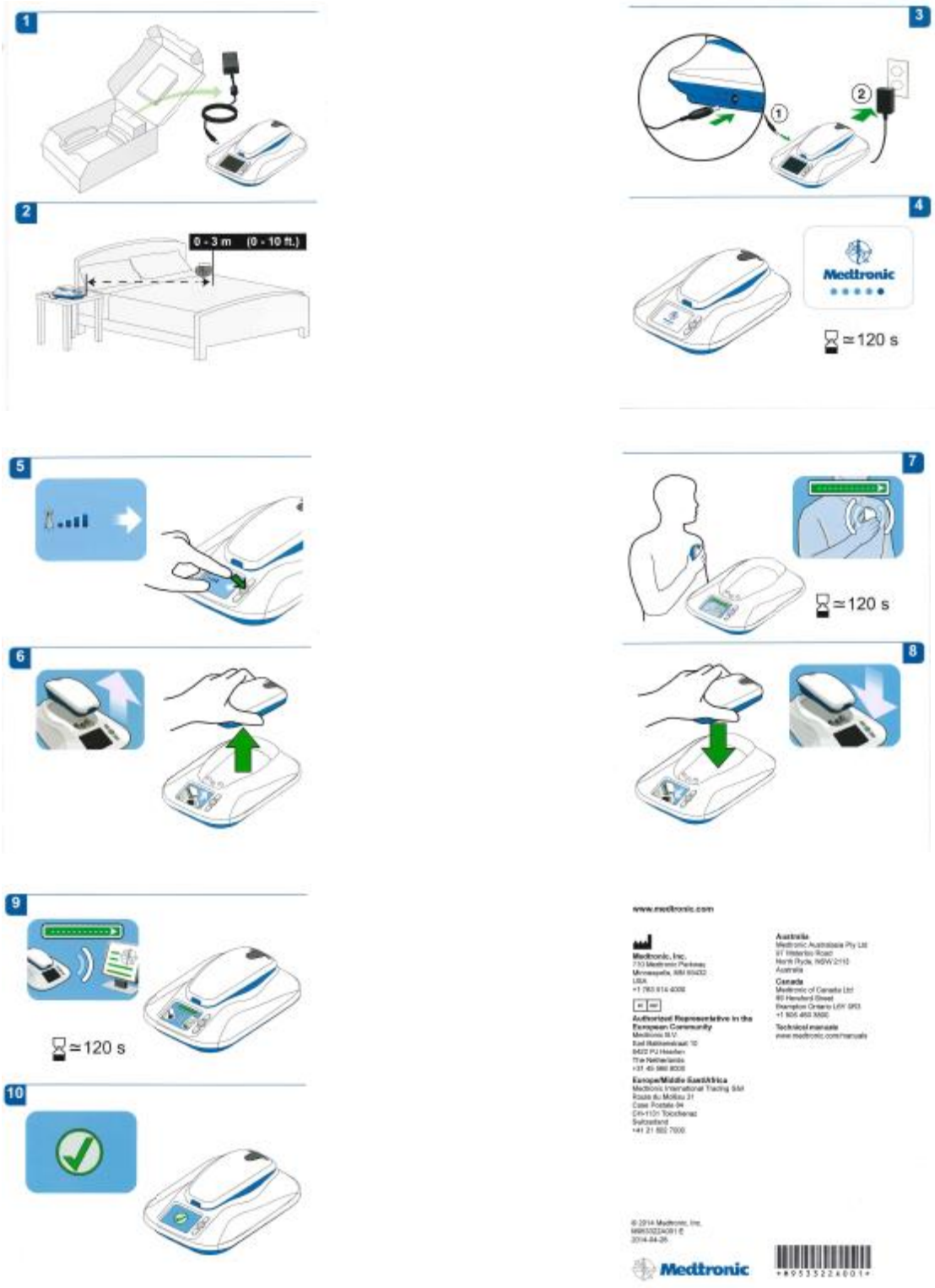
The Carelink™ network uses RF telemetry and bluetooth™ technology to retrieve information from a patient's device. The information is then transmitted across the mobile 3G network to a secure web server. Once the information is on the server it can be accessed by the patient's physiologist or

cardiologist securely by way of them logging in to a secure website. In the instance of an ILR all information that would be available in the clinic is available online, including trend tables, device parameters and ECGs. Data for European patients is stored on a server in Limburg, The Netherlands. This means that the use of this data is governed by the same data protection laws as in the UK.

The process for patients to send their information is simple; Patients press a single button on their transmitter and follow the on-screen instructions. Figure 9 shows the pictorial instruction leaflet supplied with the Carelink™ equipment. The colour illustrations match the illustrations shown on the transmitter whose screen is also in colour.

Once the information is transmitted to the server by the patient it is held until accessed by the follow-up team. In the case of CDDFT hospitals this is done daily in the morning and afternoon. Additional checks for downloads are carried out if a patient calls to notify the staff that they have had a symptom and sent a transmission or if patients call and are asked to send a transmission.

Figure 10 - Carelink™ instructions



(Permission requested from Medtronic Inc. August 2016)

2.7. Search strategy for previous research relating to implantable loop recorders in conjunction with remote monitoring

As with the previous sections of this review, all available resources were utilised in attempting to find relevant articles. PubMed, Medline, Ovid, Allied and Complimentary Medicine (AMED), Excerpta Medica Database (EMBASE), Health Management Information Consortium (HMIC), British Nursing Index (BNI), PsycInfo, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Health Business Elite were the primary search tools and databases then a search of Google Scholar was carried out as a back-up.

The search for key articles was carried out with the initial search term 'implantable loop recorder (OR) ILR (OR) implantable cardiac monitor (OR) ICM' this was followed by a separate search for 'remote monitoring'. This search was useful in highlighting the numerous applications for remote monitoring outside of the cardiology environment but was far too broad. Therefore the search was repeated as 'remote cardiac monitoring' then 'remote monitoring (AND) cardiac devices (OR) implantable loop recorders (OR) ILR (OR) implantable cardiac monitors (OR) Reveal (OR) Carelink'. After the initial search the ICM abbreviation was removed as it is used for too many other applications i.e. intensive case management, Institution of Chinese Medicine, ischaemic cardiomyopathy, in chair movement, and Institute for Complementary Medicine. The search including 'ICM' returned over 17,000 articles whereas the search minus 'ICM' returned a more manageable 2,300 articles. Details of the search strategy and number of results can be found in Table 2 - Search databases, terms, and number of results.

Table 2 - Search databases, terms, and number of results

Database(s)	Search term	No. of results
AMED, BNI, CINAHL, EMBASE, HBE, HMIC, Medline, PsycINFO, PubMed	(Implantable loop recorder OR ILR OR implantable cardiac monitors OR ICM).ti,ab	17,269
	(Implantable loop recorder OR ILR OR implantable cardiac monitors).ti,ab	2,315
	(Remote monitoring).ti,ab	8,837
	(Cardiac remote monitoring).ti,ab	389
	(remote monitoring AND (cardiac devices OR implantable loop recorders OR ILR OR implantable cardiac monitors OR Reveal OR Carelink)).ti,ab	536

Inclusion criteria for articles / papers:

1. Article / paper must be directly related to the use of remote monitoring in conjunction with ILRs.

2. Article / paper must be written in or translated to English.

After the search had been altered to remove the ‘ICM’ abbreviation a brief review of all the returned titles of the articles / papers was carried out. If a title suggested relevance then the abstract was also reviewed and in some cases the full text was reviewed. All articles that did not stipulate in the title what type of device was used or whether remote monitoring was used then the abstract was reviewed. The search was carried out using the term individually and in conjunction with one another to ensure nothing pertinent to the investigation was missed. When the final search was carried out, of the initial 533 articles there were 129 duplicate articles which were removed, this left 407 articles. Once all of the 407 articles had been reviewed and the inclusion criteria applied, only three articles were identified. In addition to the three, there were previously published conference proceedings appearing on searches, however on attempting to obtain these publications they could not be obtained. Even going direct to the journals involved became a fruitless exercise as the supplements that had published the work had been removed for reasons unknown. Initially the lack of publications was a shock, but considering the narrowness and relatively young age of this topic, perhaps this is an expected result.

The three relevant articles returned as of May 2017 were:

1. Remote electrocardiographic monitoring with a wireless implantable loop recorder: minimising the data review burden (45)

2. Effectiveness of remote monitoring in the management of syncope and palpitations (44)

3. Effectiveness and safety of remote monitoring of patients with an implantable loop recorder (68)

All three of the reviewed and appraised articles were written by authors with affiliations to well-known institutions and were published in peer-reviewed journals.

2.8. Article One - Remote electrocardiographic monitoring with a wireless implantable loop recorder: minimising the data review burden

The first article by Arrocha and colleagues (45) reported the findings of 'The pilot study of the Sleuth® implantable ECG monitoring system (PULSE)'. PULSE was a non - randomised, prospective pilot study. It was designed to gain proof of concept for a novel wireless ILR with a non-patient interactive remote monitoring system in a clinical setting therefore did not incorporate a control group.

Whilst the equipment used in this study was significantly different to the Medtronic Inc. equipment, in terms of device size and patient interaction, it

was the first study to look at remote monitoring of ILRs and it raised some interesting questions surrounding the burden that increased follow-up of ILRs will create for clinical staff, regardless of whether follow-up is remote in nature or not.

The PULSE study recruited 40 patients from four centres with unexplained syncope suspected to be cardiac in origin of whom the most recent 12 lead ECG showed normal sinus rhythm. Unfortunately the article did not state if the patients were recruited consecutively or if there was any form of further inclusion or exclusion criteria applied to participants. The omission of any form of selection criteria or selection process for the PULSE study raises the question of selection bias. The report only stated that the participants' last 12 - lead ECG showed normal sinus rhythm plus or minus ectopic beats; it did not report any other tests that were carried out and raises the question of whether the researchers were allowed to select their patients.

The paper states that the devices were programmed at the physicians' discretion but the analysis criteria was set out by the researchers: the paper does not give any further details as to what parameters were at the physician's discretion. The researchers chose for their automated detection for bradycardia only one beat below 40bpm as a trigger and six out of eight beats above 150bpm as a tachycardia. The manual review was perhaps a little more stringent but in the majority of cases in our clinical practice for example a bradycardia would not be considered significant unless it was less than or equal to 30bpm for four or more beats. Whilst this may miss some arrhythmias the primary function of a loop recorder is to correlate symptoms

with the presence of arrhythmias or to confirm that arrhythmias are not present at the time of symptoms and therefore rule in or out a cardiac cause for a patient's symptoms. However, the bradycardia settings in the PULSE trial were the same as those suggested by the ISSUE investigators (69) and the research undertaken in this literature review suggests that it is our practice that needs reviewing. One would also have to question the tachycardia and asystole settings from the PULSE study as even at the manual review stage, tachycardias above 150bpm and asystoles greater than two and a half seconds were passed to the physician for further assessment, a point that may have affected the outcome of the study. Their extended manual criteria for supraventricular tachycardias (SVTs) of greater than 30 seconds, (accelerated) idioventricular rhythm greater than ten beats, ventricular tachycardia (VT) greater than four beats, ventricular fibrillation/flutter (VF), torsades de pointes and any second degree heart block with bradycardia or complete heart block/atrioventricular dissociation were clinically sound.

The results of the study showed that 223,226 ECGs were recorded over a mean eight and a half month follow-up period, which equated to an average monthly auto-detection of 685 ECGs per patient. However only 117 relevant ECGs were found out of the 223,226 that were recorded which leads on to the conclusion of the study. The researchers concluded that remote monitoring of ILRs may create excessive burden but that a sensitive detection criteria was still preferable in order to reduce the chance of missing arrhythmias and that they found relevant ECGs for 50% of their study patients. Unfortunately they did not state whether 'relevant' ECGs equated to a diagnosis. Neither did they allude to what the breakdown of the recordings was so it may actually

have meant that a recording of sinus bradycardia at 39-40bpm was recorded nocturnally in an asymptomatic patient and in reality none of the patients received a diagnosis.

2.9. Article Two - Effectiveness of remote monitoring in the management of syncope and palpitations

Article two by Furukawa et al (44) reported the use of Reveal™ and Carelink™ for the clinical management and acceptance of patients with syncope and palpitations.

This was a multi-centre, prospective, non-randomized study which recruited 47 consecutive patients who were over 18 years of age that had suffered from two or more episodes of unexplained syncope or palpitations.

Patients in this study all received a Reveal™ DX or XT ILR and a Carelink™ home monitoring system. Participants were asked to transmit the data from their ILRs on a weekly basis and on the day of any symptoms which resulted in a manual recording. This method, whilst possibly eliminating the device's memory saturation and reducing the time to detection of an automated recording, has the potential to create excessive additional workload for physicians and physiologists. Weekly downloads it might also be argued go against the current guidelines of the National Institute for Health and Clinical Excellence (NICE) (4), and the European Society of Cardiology (ESC) (5) which suggest that ILRs should only be implanted in patients that have infrequent symptoms (less frequently than fortnightly). This may be a prudent point to keep in mind as we move through the review of this article.

The researchers evaluated their data against an established and well-reviewed standard, developed by the International Study on Syncope of Uncertain Etiology (ISSUE) investigators (69).

Unfortunately there was no control group for this study: in order to overcome the lack of a built-in study control the researchers used previously published data to draw comparisons against their data. This promotes several issues; firstly the data may be out-of-date so comparisons are already slightly biased and secondly due to differences in measurements the comparisons that can be drawn and statistically tested may become limited. It is important to mention that the reporters were also aware of this and made reference to this shortcoming in their limitations section. Unfortunately they then tried to say that this would only affect the results on diagnostic yield and the study was aimed at effectiveness and acceptance. This perhaps is mildly deceptive on the researchers' behalf as they also used the published data to compare the time taken to reach a diagnosis which was one of their primary markers for effectiveness.

The results of this study state that they received true relevant ECGs in a median of 11 days, this suggests that some of their patients may have only required extended external ECG monitoring with an event recorder or Holter monitor. However later on in the report the researchers do state that a 'True relevant ECG' is not the same as a diagnosis and that they 'estimate' a reduction in time to diagnosis of 71 ± 17 days.

One of the significant findings of this study was the acceptance factor of the Reveal™ ILR in conjunction with Carelink™ as it suggests that remote monitoring of ILRs is well accepted and that 70% of the study patients actually felt safer with the addition of Carelink™. To date there is no literature available via searches of PubMed or Medline relating to the psychological impact of ILRs, in terms of waiting for another symptom to occur so that the medical team can observe, and whilst it is outside of the remit of the Real Care study it is the author's opinion that this is an area which warrants further qualitative investigation, even if it focuses solely on the patient perspective of ILRs with the addition of remote monitoring.

The researchers of the effectiveness of remote monitoring in the management of syncope and palpitations paper (44) concluded that remote monitoring is a powerful additive tool to use in the unexplained syncope and palpitations ILR population. Carelink™ is well accepted and weekly transmissions are optimal for the majority of patients. From researching the previously reviewed papers (44,45) and from clinical experience the author suggests that weekly downloads may create an excessive burden on patients and clinical staff whilst potentially not offering a significant improvement in diagnostic capabilities of ILRs.

2.10. Article Three - Effectiveness and safety of remote monitoring of patients with an implantable loop recorder

The third and final paper (68) to be reviewed was perhaps the most robust and the only one to openly admit the presence of time and selection bias.

The reporters did try to play this down by saying that the baseline characteristics were similar and that their cohorts were implanted sequentially.

The effectiveness and safety of remote monitoring of patients with an implantable loop recorder study was a single-centre historical cohort study comparing data collected from a group of ILR patients without Carelink™ (control) and a group of ILR patients with Carelink™. The control group in this study had in-office follow-up with device interrogation and clinical assessment at three-monthly intervals while the Carelink™ group sent monthly transmissions or transmissions within 24 hours of a symptomatic episode. The Carelink cohort also had a two-way telephone contact service available in case of syncope or a significant event.

Their study included all patients that had a Medtronic Reveal™ DX or XT between January 2003 and December 2010. In total there were 109 patients in this study broken down to 41 in the control group and 68 in the Carelink™ group. The control group patients received their devices between January 2003 and October 2010 and the Carelink™ group were implanted between June 2009 and December 2010.

The study analysed for the most part the same variables as the previous studies (age, gender, number of recordings, number and type of both true and false recordings, time from event to follow-up, and time to diagnosis) and also used the ISSUE (69) classification to categorise and determine whether an ECG was significant or not. In addition to this they also looked at the type and frequency of visits that patients made to the hospital in order to see if remote

monitoring of ILRs affected hospital presentations and which mode of presentation has the most significant alteration. Finally the researchers looked at the time not only to diagnosis but also to the time to initiation of treatment and the specific treatment prescribed in response to a significant ECG.

This was the only study of the three to use statistical tests to measure the significance of their results; the researchers stated that they used the Mann-Whitney U test for non-parametric results and the Pearson chi-squared test for frequency data. However they also stated that the frequency data was qualitative not quantitative, therefore they would not have been able to use the Pearson chi-squared test unless their qualitative work was a hybrid of qualitative and quantitative research and used a Likert scale. While the use of Likert scales is commonplace in research there are those hard-core qualitative researchers that would state that this is in fact quantitative in nature as it can be statistically analysed. It is more likely however that this is due to a typographic error, a translational error as the original article was written in Spanish, or it could be a reflection of the peer review process.

The researchers concluded that the use of remote monitoring enhanced the diagnostic ability of ILRs by reducing the time taken to encounter a significant event and also reach a diagnosis, therefore reducing the time taken to implement a specific treatment. The researchers reported that the time taken from implant of the ILR to diagnosis of a significant event was 56 (0 - 650) days vs 260 (5 - 947) days $p < 0.01$ and that the time device implant to initiating treatment was significantly different at 73 (0 - 650) days vs 260 (5 -

947) days for remote monitoring and conventional care respectively ($p < 0.01$). The study also highlighted that the use of remote monitoring effectively reduced the number of planned and unplanned visits not only to cardiac diagnostic units but also to accident and emergency departments.

2.11. Summary of the key evidence

All of the studies made some valid points but none of them were without their flaws, primarily this was down to one or all of the following:

1. Lack of a control groups - studies one and two

2. Non-concurrent control group - study three

3. None of the studies had any randomisation

Coupled with the above problems was the inherent potential for bias to influence the interpretation of the studies. On the whole the reporters were open about the limitations but in all cases attempts were made to either justify the areas liable to bias or play down the problems that could arise.

All of the studies were in favour of the use of remote monitoring with ILRs but there is too much left to chance for certainty and a powered fully randomised and controlled study that minimises the possibility of bias and chance findings is the only way to be sure that remote monitoring does not become a service that is draining healthcare resource without improving the diagnostic services provided.

While there is a plethora of information and research surrounding the ILR itself, it appears from the literature that we as clinical healthcare professionals are either happy to accept the addition of new technology without robust research or that we are going the other way and refusing to accept that there may possibly be a better way to look after our ILR patient population.

2.12. Summary of the chapter

Syncope and palpitations are symptoms that can potentially have life threatening consequences and a negative impact on patient's lives in terms of anxiety and lifestyle if undiagnosed. Unfortunately diagnosis of the underlying cause can be prolonged simply by the test employed and the frequency of the symptoms. The evidence presented in this chapter suggests that ILRs are a valuable and effective tool for either diagnosing a cardiac cause for symptoms or ruling out a cardiac cause for symptoms. That same evidence suggests that whilst the ILR is an effective tool it can still be a lengthy pathway. However, ILRs in conjunction with remote monitoring has shown potential in reducing the diagnostic time for patients with syncope and palpitations, therefore ensuring that patients receive the correct treatment without delay. Whilst the evidence suggests a potential to reduce diagnostic time there is not enough data prove this.

The literature review, particularly the three articles reviewed highlighted that a more robust study was required. The REveAL™ and Carelink™ (Real Care) study was designed as the first prospective, randomised, clinician blinded, controlled trial in this field to address the lack of robust evidence relating to remote monitoring of ILRs.

Chapter 3. Real Care study aims, objectives, design and implementation

In this chapter the aims, objectives and full methodology including the REveAL™ and CARElink™ (Real Care) study design are covered. The protocol for the study can be found in Appendix 1.

3.1. Aims of the Real Care study

The primary aims of the Real Care study were to ascertain if:

1. The average time to follow-up from a true event occurring can be reduced if remote monitoring is included in the patients care pathway.

2. The average time taken to achieve a diagnosis in the implantable loop recorder (ILR) population could be reduced with the use remote monitoring equipment.

The secondary aims for this study were to ascertain:

1. How much data is generated for review (review burden) by true and false recordings, both with and without the use of remote monitoring?

2. Does remote monitoring impact ILR memory saturation?

3. Can age or gender be used as determinants to predict diagnosis?

4. What CDDFT's ILR diagnostic yield is.

5. What is the trigger for true and false ILR recordings in terms of arrhythmia, artefacts or signal sensing and how do they breakdown into diagnosis?

6. How long does it take to record the first true event?

7. What the primary implant indications are in CDDFT hospitals?

8. What is the response to diagnosis (in terms of monitoring)?

The secondary aims are split into sections; the first two of the secondary aims are assessing the impact of remote monitoring on clinical activity and device memory. It was suggested by Arrocha and colleagues (45) that remote monitoring could create an excessive amount of data to be reviewed and by Furukawa and colleagues (44) that remote monitoring could almost eliminate ILR memory saturation therefore minimising potentially missed true events.

The next section of the secondary aims (secondary aim 3) was aimed at discovering whether age or gender can be used as predictors of diagnosis, this would be of particular interest if remote monitoring proved to be superior in the primary aims but created excessive data and therefore needed a selection criterion. For example, if patients in the 30-50 year old age group were more likely to receive a diagnosis then perhaps they should be targeted with home monitoring first.

The final section of the secondary aims (secondary aims 4 - 8) will assess the not only the diagnostic yield but what the actual recordings were from the patients in the Real Care study in terms of arrhythmias, artefacts, and sensing issues such as signal dropout and how they breakdown into diagnosis? Moving on to assess whether CDDFT is implanting devices for appropriate reasons and what in terms of monitoring strategy (i.e. explant or continue to monitor) is the response to diagnosis. Whilst this final section of the secondary aims could potentially be seen as audit data it is also important information when considering the effectiveness of remote monitoring as the results could be skewed if the implant data and diagnostic yield were inappropriate.

3.2. Objectives of the Real Care study

The primary aims were to be achieved by collecting the follow-up data of the control and experimental groups of ILR patients that participated in the Real Care study and statistically analysing the data to determine if there was a significant change in the time taken to reach a diagnosis, be it a cardiac or non-cardiac diagnosis.

The secondary aims were to be achieved by collecting data and analysing the results using descriptive statistics, and comparing group data statistically where possible. Cox regression will be used to see if age group, gender or study group used as determinants affected the hazard ratio (HR) of a diagnosis being reached with the use of an ILR.

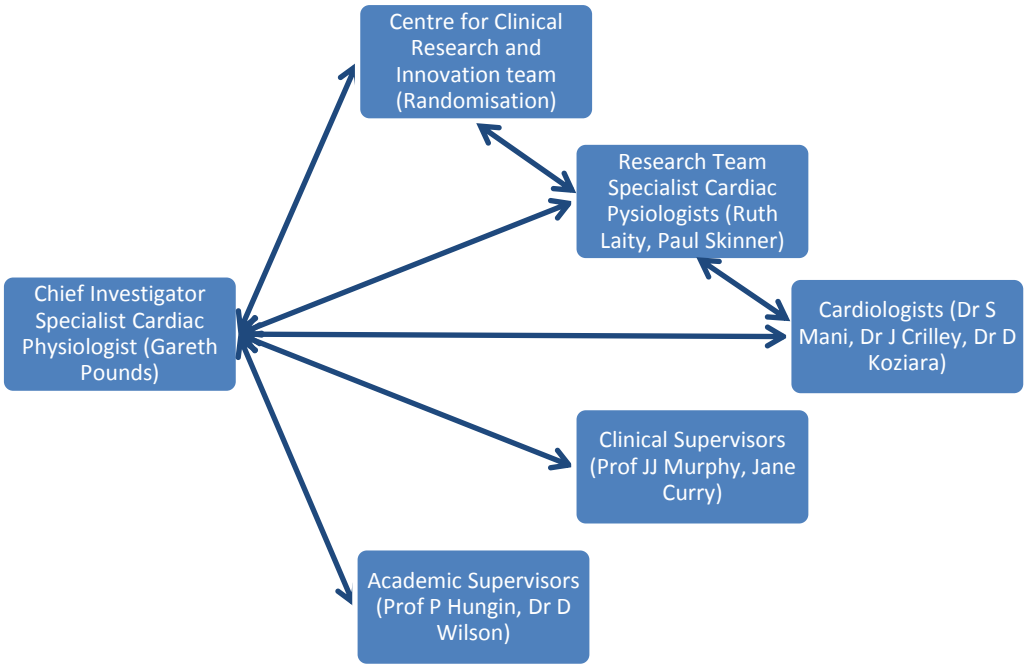
3.3. Study design, setting the scene

The Real Care study was a prospective, randomised, clinician-blinded study carried out within County Durham and Darlington NHS Foundation Trust (CDDFT), using consecutive and informed patients who received an implantable loop recorder (ILR). The three main sites of the Trust in which research activities were carried out were the Cardiac and Respiratory Services Departments at Darlington Memorial Hospital (DMH), Bishop Auckland General Hospital (BAGH) and University Hospital of North Durham (UHND). This included the two Cardiac Catheterisation Laboratories (Cath Labs) at DMH and UHND. Data analysis was carried out on an intention-to-treat basis; therefore all the results of the patients who completed the study were analysed in their respective group, regardless of crossover or non-compliance.

3.4. Research and study team structure

Figure 11 shows the structure of the research team including those directly involved in the study and the supervisors. The interaction points are also highlighted with arrows.

Figure 11 - Research / Study team stucture



3.5. Ethical approval

The Real Care study received favourable ethical opinions from the Northeast Regional NHS Ethics Committee and the Durham University's School of Medicine, Pharmacy and Health Ethics Committee.

3.6. Trial registration

The Real Care trial was registered with the International Standard Randomised Controlled Trial Registry and the International Standard Randomised Controlled Trial Registration Number (ISRCTN) is ISRCTN72340423.

3.7. Training

Before carrying out research or to be involved in research within the NHS in England, it is a requirement that researchers and members of staff

undertaking any research activities have completed the Introduction to Good Clinical Practice in Research (GCP) programme. All members of the research team for the Real Care study completed this before commencing any research activity related to the study. All members of the team also completed and passed the beINFOrMED online consent training and assessment programme and the participating physiologists all held or were working towards their British Heart Rhythm Society (BHRS) formerly Heart Rhythm UK (HRUK) accreditation in cardiac rhythm management (CRM) devices.

The Chief Investigator (CI) and author also attended courses on quantitative research, qualitative research, basic statistics, logistic regression, syncope courses, and cardiac educational seminars and conferences (national, local and industry).

3.8. Patient involvement

The patient information sheet (PIS) (Appendix 2) was reviewed informally by patients attending the devices clinic and it was decided that a formal arrangement for patient involvement was required.

A Patient Advisory Group (PAG) consisting of four patients was formed. This group consisted of previous and current ILR patients both with and without Carelink™ experience. The PAG was asked to review any changes to the PIS and supporting information. They were also asked if they would be willing to assist with any patient concerns that may have arisen. The members of the PAG were chosen based on not only their expertise but also on the value it was felt that they could add to the study.

Letters were sent to the proposed members of the PAG asking them if they would be interested in assisting with the study. If they were keen to take part they were asked to attend a meeting at their local CDDFT hospital where they were fully informed of the study and their role as a member of the PAG. The meeting was hosted by the CI who also informed them that their involvement was entirely voluntary and that they were free to leave the group at any time.

There was no provision for financial gain for PAG members but travelling expenses for PAG duties such as meetings were paid in line with current CDDFT allowances. Additionally, refreshments were provided at meetings.

Participants in the Real Care study were given the contact details of an independent person that was available to answer questions on research in general and mediate if the participant had any concerns that they did not wish to directly speak to a researcher about.

3.9. Recruitment – Who and How?

Historic implant and growth rates were used to predict that 95 ILRs would be implanted in the 2012/13 financial year with a further significant increase in the 2013/14 financial year. Due to the previous implanting data and subsequent predictions, a recruitment period of 24 months was allowed for the Real Care study.

In order to reduce patient selection bias that could be created by physiologists only choosing patients that they felt might have a positive outcome, all patients that received an ILR at one of the CDDFT Catheter Laboratories

were given a brief verbal description of the Real Care study and asked for verbal consent for a PIS being posted to their home address prior to their first follow-up.

Following an amendment to the protocol which was approved by the ethical committees mentioned in section 3.4 the recruitment process was altered so that patients received a PIS prior to the day of implant. This was given at the pre-assessment appointment allowing the patient time to read the information and have a minimum of a 48 hour cooling off period. Patients were asked on the day of their implant if they would like to take part in the study. If they agreed, the consent form (Appendix 3) was signed and the randomisation was carried out providing that the patient was eligible against the inclusion and exclusion criteria. In some instances the patient asked for more time to consider their position, in these instances the patient was asked again at their first follow-up.

Recruitment to the Real Care study was slower than originally anticipated, the problem with this was believed to be the protocol issue and would be resolved by the amendment made to the way in which patients received the PIS. Whilst the amendment did increase the recruitment rate, there were still a large number of patients not entering the study.

In total 185 patients received a PIS, 148 (80%) of those were not included in the study. Of that 148 patients, 28 (19%) patients did not meet the inclusion criteria (Section 3.10) (this included ten patients that received a different ILR device) and 31 (21%) declined to participate. That left 89 patients which was

48% of the overall number of patients that received a PIS, not included in the study and 37 patients that entered randomisation. The issues that impacted the recruitment rate are covered in more detail in the discussion in Chapter 7.

The breakdown of the 37 patients randomised was, 19 to the control arm and 18 to the experimental arm with one patient initially non-compliant and then lost to follow-up in the experimental arm. A further two patients that, whilst they did comply with the use of the equipment in the experimental arm, they missed transmissions on a regular basis.

Figure 12 shows a graph of the planned recruitment and the actual recruitment to the Real Care study over the 24 month recruitment period.

Figure 12 - Graph showing actual and predicted patient recruitment to the Real Care Study

Analysis of the age and gender profile of the patients not included in the study showed no statistically significant differences when compared to those that were included in the Real Care study.

3.10. Inclusion Criteria

The inclusion criteria for patients implanted with a Medtronic ILR device at CDDFT hospitals were that they:

1. Were aged 18 years or over

2. Had access to a landline telephone

3. Were themselves cognitively capable to consent

4. Had the ability to use the manual activator and Carelink™ equipment or had a willing and appropriate adult to do so for them

5. Were able to communicate and understand instructions given in English

The reasoning behind the final point on the list is that due to this being a Trust or 'in-house' funded study the financial provision was not available to have translators available for fortnightly follow-up in the experimental patient group. Nor was it financially viable to have the literature published in multiple languages.

3.11. Exclusion Criteria

Patients were excluded from the study if:

1. They did not have access to a landline telephone

2. They had documented cognitive impairment that meant that they were unable to consent

3. Were unable to comply with the use of any equipment

4. Patients that were considered for Carelink™ for geographical reasons e.g. living in the secluded villages within the CDDFT catchment

5. They could not communicate or understand instructions given in English

3.12. Sample size considerations

The sample size required for this trial was calculated using data collected in an audit of CDDFT ILR patients on conventional follow-up, and a decision made by the research team, that in order to make a trust-wide remote monitoring service viable a reduction in diagnostic time of 50% was required. Data from a recent service evaluation suggested that a 50% reduction was a realistic possibility. The service evaluation used the data from 16 patients put prospectively on to the remote monitoring system and compared it to retrospective audit data from ten years of previous ILR implants within CDDFT hospitals. ILR patient files were excluded if they were incomplete, received a device other than a Medtronic™ ILR, or if they had no floppy disk containing

their ILR recordings and data present. In total there were 112 files included in the retrospective data collection. The audit and service evaluation were carried out in 2012 by Gareth Pounds (author of this thesis).

Data from the retrospective audit indicated that 85% of patients on conventional (control) ILR follow-up had not received a diagnosis after 12 months. After clinical discussion it was adjudged that this could be reduced to 43% of the patients, using Carelink™ remote (experimental) follow-up over the same time period. Using the software program nQuery7 and a log rank sample calculation for proportional reduction a total of 52 patients were required to enter this study, 26 patients into the control arm and 26 patients into the Carelink™ arm. The alpha (α) error was set to 0.05 and the beta (β) error was set to 0.1, giving a two tailed significance of 5% and a power of 90% [100(1 – β)], see Table 3 - nQuery7 output.

Table 3 - nQuery7 output

Two group χ^2 test of equal proportions (odds ratio = 1) (equal n's)	
Test significance level, α	0.050
1 or 2 sided test?	2
Group 1 proportion, π_1	0.850
Group 2 proportion, π_2	0.430
Odds ratio, $\psi=\pi_2(1-\pi_1)/[\pi_1(1-\pi_2)]$	0.133
Power (%)	90
n per group	26

As a precaution to allow for dropouts and loss to follow-up, an additional 10 patients per group were added into the calculation. This gave a total of 72 patients in the study, 36 patients per group.

The sample size decisions were reviewed and approved by Dr Douglas Wilson, Statistician at Durham University, School of Medicine, Pharmacy and Health.

3.13. Treatment arms

The Real Care study consisted of two treatment arms, a control arm and an experimental arm. Patients randomised to the control group were followed up in the conventional manner within CDDFT hospitals. The patients were seen in the clinic five weeks post implant and then at six-monthly intervals or if they had suffered three symptomatic episodes or one episode that they were particularly concerned about. At each follow-up for control group patients, the patient had their ILR interrogated and any stored ECGs were classified according to the Real Care classification table (Table 4) adapted from the table created by the International Study on Syncope of Uncertain Etiology (ISSUE) investigators (69) (Figure 13 - The ISSUE Classification table taken from Brignole et al 2005 . This was the same process regardless of whether it was a standard six-month appointment or an additional appointment due to the patient having the symptoms associated with their implant, such as syncope, severe dizzy spells or palpitations. All data was then stored electronically to ensure that classifications could be verified at a later date.

The experimental arm patients received the same five week and six-monthly appointments as the control arm patients but in addition to this they received the Carelink™ remote monitoring equipment. The equipment was demonstrated when it was issued and also had simple instructions supplied with it (Figure 10). Patients were asked to send their data at fortnightly

intervals and send additional transmissions if they had a symptomatic episode. Any ECGs which had been downloaded and transmitted were classified using the same criteria as the control patients. All transmissions were stored on the Carelink™ network and were also stored as PDFs on the CDDFT servers in order to avoid data loss in the event of a network failure and to allow for later verification.

3.14. Procedure for all follow-ups with significant ECGs

If a patient presented to follow-up (in-office or remote) with a clinically significant ECG recording, the physiologist printed the recording, removed the identifiable data, and labelled the printout with the patient's study number. A cardiologist was then asked to review the recording along with symptom data. If the patient required any form of intervention as a direct result of the recording then this was considered to be a diagnosis and the patient was removed from the study.

Table 4 - The Real Care Classification of ILR ECG Recordings

True Events	False Events
FVT or VT recording showing a tachycardia ≥120bpm, conclusively or believed to be a rhythm other than sinus tachycardia.	FVT or VT recording showing sinus tachycardia or artefact.
Asystole recording showing an R-R pause of ≥3 seconds (for AF ≥3 seconds diurnally and ≥4.5 seconds nocturnally)	Asystole recording with evident under-sensing.
Bradycardia recording with a sudden decrease in heart rate of >30% or <40bpm for ≥10 seconds.	Bradycardia recording with evident under-sensing.
Manual recordings displaying any of the above, or manual recordings showing no significant ECG changes / false events but recorded in the presence of patient symptoms.	Manual recordings displaying any of the above, or no significant ECG changes if recording is made in the absence of symptoms or in the presence of symptoms not related to ILR implantation.

Figure 13 - The ISSUE Classification table taken from Brignole et al 2005 (69).

Table 1 The ISSUE classification of ECG-documented spontaneous syncope

- *Type 1 Asystole*. RR pause ≥ 3 seconds
  - → *Type 1A, Sinus arrest:*
    - – Progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest
  - → *Type 1B, Sinus bradycardia plus AV block*
    - – Progressive sinus bradycardia followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate
    - – Sudden onset AV block (and ventricular pause/s) with concomitant decrease in sinus rate
  - → *Type 1C, AV block*
    - – Sudden onset AV block (and ventricular pause/s) with concomitant increase in sinus rate
- *Type 2, Bradycardia*. Decrease in heart rate >30% or <40 bpm for >10 seconds
  - → *Type 2 A*. Decrease of heart rate >30%
  - → *Type 2 B*. Heart rate to <40 bpm for >10 seconds
- *Type 3, No or slight rhythm variations*. Variations of heart rate <30% and heart rate >40 bpm
  - → *Type 3 A*. No variation or <10% variation in heart rate
  - → *Type 3 B*. Increase in heart rate >10% but <30% and <120 bpm; or, decrease >10% but <30% and >40 bpm
- *Type 4, Tachycardia*. Increase in heart rate >30% or >120 bpm
  - → *Type 4 A*. Progressive sinus tachycardia
  - → *Type 4 B*. Atrial fibrillation
  - → *Type 4 C*. Supraventricular tachycardia (except sinus)
  - → *Type 4 D*. Ventricular tachycardia

(Permission requested from the ISSUE reporters)

3.15. Endpoints and outcomes

The clinical endpoints of this study were:

1. Time to diagnosis/outcome

2. Device removal for any reason

3. Death

For an endpoint to be considered it had to occur within the 24 month follow-up period of the study.

Primary outcomes were classed as positive, negative or none. A positive outcome was for patients that receive a cardiac diagnosis, a negative outcome was for patients who could be confirmed not to have a cardiac cause for their symptoms and none was for the few patients who did not have a symptom or true event during the follow-up period.

3.16. Randomisation

Once patient consent and eligibility to join the trial were confirmed they were allocated a study number and randomised to either the control arm or Carelink™ (experimental) arm. Randomisation was carried out in a block randomisation method using mixed blocks of four, six and eight on a 1:1 basis in order to maintain similar patient numbers in each group.

A randomisation table was generated by Dr Douglas Wilson, Statistician at the School of Medicine, Pharmacy and Health (SMPH) at the Durham University and held by an independent staff member within CDDFTs Clinical Innovation and Trials Unit (CITU). Researchers contacted this team once a patient was enrolled. The patient was then allocated a study number which was compared to the randomisation table by the independent staff and the patient was allocated to the control or experimental arm. All correspondence was logged and researchers at no point had access to the randomisation table.

The point of randomisation in the patient's journey can be seen in Figure 14 - The Real Care patient care and data collection pathway on page 90

3.17. Protocol amendment

There was one amendment made to the Real Care protocol after the initial favourable ethical opinions were granted. The amendment was related to recruitment and was considered to be minor changes which received continued ethical support. More specifically the amendment altered the way in which patients received the PIS. Originally patients received the PIS through the post after giving verbal consent to receive one on the day of implant. The amended protocol meant that patients were given a PIS at their pre-operative assessment (two – seven days prior to implant) and were asked to consent on the day of ILR implant.

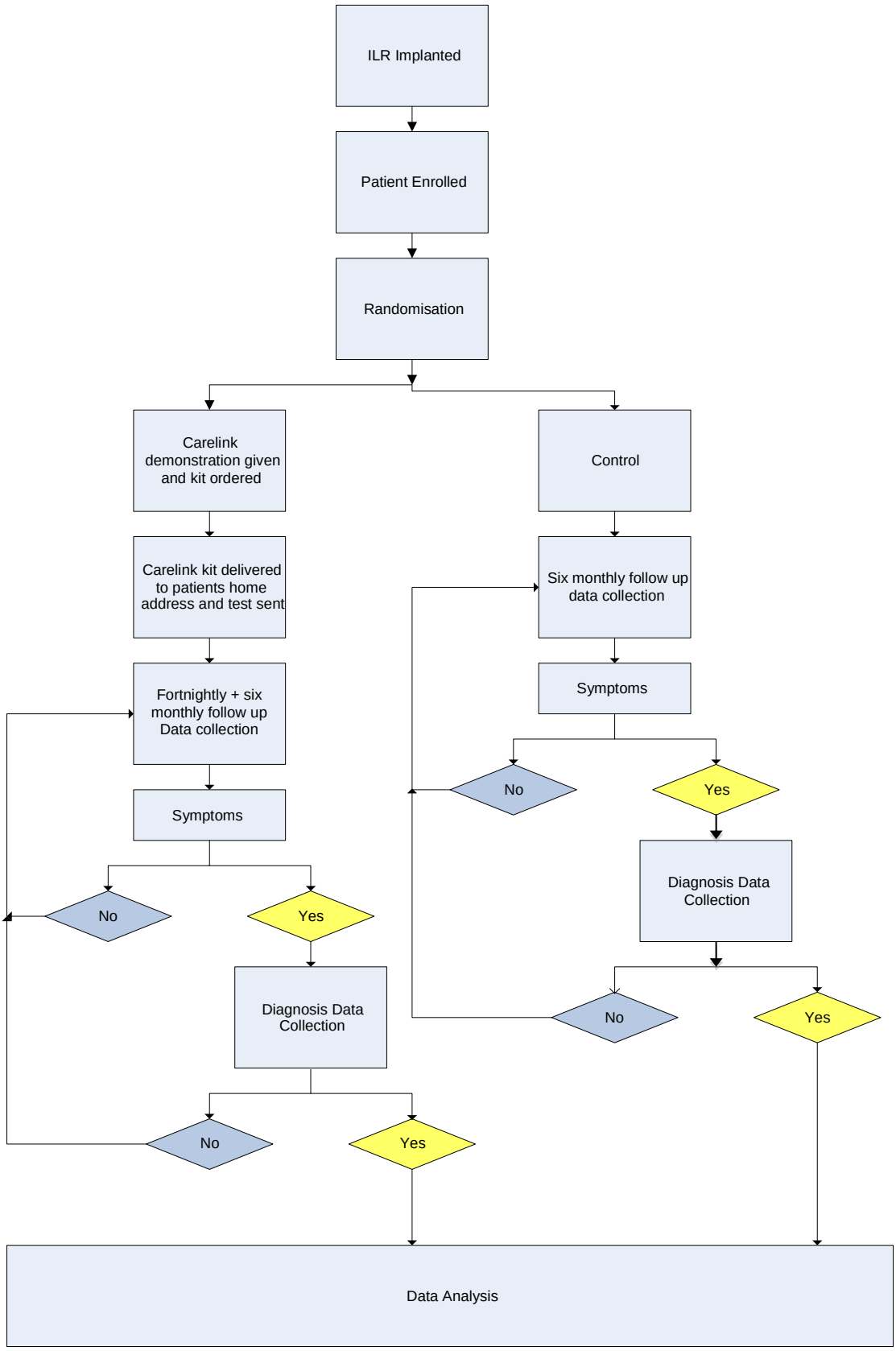
Chapter 4. Data collection, storage, verification, security and timelines

In this chapter the patient care and data collection pathway for the Reveal™ and Carelink™ (Real Care) study is presented. The storage of data and the method of verification of data are described and the security of both identifiable and non-identifiable data will be explained.

4.1. Patient care and data collection points for the Real Care study

Figure 14 - The Real Care patient care and data collection pathway illustrates the patient care pathway followed during the study, including the data collection points and decision processes used.

Figure 14 - The Real Care patient care and data collection pathway



4.2. Data verification and storage

All follow-up data from implantable loop recorders (ILRs) implanted into patients participating in the Real Care study was stored either to 3.5 inch floppy disk (control arm) or on Medtronic Inc.'s secure servers in The Netherlands (experimental arm) along with the follow-up forms filled in by the physiologist during the follow-up. The use of 3.5 inch floppy disks is an 'old fashioned' practice and one that is becoming increasingly difficult to use as local Information Governance (IG) policies demand more secure methods of data storage. However, the Medtronic™ 2090 model programmer will not accept secured or encrypted USB memory drives and these are the only other storage media currently available within the Trust (It is worth note at this point that Medtronic Inc. are currently working on a new generation of programmer which will be able to connect to the hospital WiFi, allowing data transfer directly to a sever within the trust or to the Carelink™ network). The raw data stored on the floppy disks is encrypted and can only be read by a Medtronic™ programmer. As data was transferred to the data collection spreadsheet the chief investigator (CI) checked all ECGs from all follow-ups and verified the report made. If the CI was the initial reporter then the ECGs were verified by another physiologist (Ruth Laity, Paul Skinner or Jane Curry) thus ensuring that all ECGs were verified. If there were any discrepancies or disagreement on ECG classification then the ECGs were reviewed by another physiologist and the majority consensus was used. There were only nine events during the entire study that required discussion but due to the nature of the potential discrepancy, the discussion was carried out during the follow-up as it could have altered the action taken at that time. For example signal dropout can on occasion look like asystole and vice versa.

4.3. Data security and anonymisation for the Real Care study

All relevant data were transferred from the patient's medical notes and the departmental loop recorder file on to an analysis spreadsheet (spreadsheet A). This spreadsheet held only non-identifiable patient data. During the collection process the patient's study number was used to link the patient to the spreadsheet. A second spreadsheet (spreadsheet B) containing all patient identifiable data used in the study (name, date of birth and hospital number) was also created. Once the study was complete spreadsheet B containing the patient identifiable data was destroyed and patient study numbers were removed from spreadsheet A containing the analysis data. Patients who requested copies of the findings of the study had their contact details retained until they received their copies of the appropriate study reports.

All spreadsheets were created and managed by the Chief Investigator (CI) who also had overall responsibility for ensuring patient data was handled appropriately and that only anonymised data were presented or disclosed to those outside of the research team and the direct care group. The Clinical Innovation and Trials Unit (CITU) within the Trust held the randomisation tables with patient initials and date of birth.

4.4. Data and Data Protection

During the trial patient identifiable data was available to the CI and clinical staff directly involved in the patients care only. Once data had been anonymised it was available to the CI and the study's supervisors. All patient information was accessed and handled in a confidential manner throughout and any hard copies of data were stored in locked filing cabinets in locked

departments at one of the research sites. All electronic information that contained patient identifiable information (PII) was stored on password protected networked CDDFT PCs, CDDFT encrypted laptops or Medtronic's secure server. Anonymous data was stored on password protected networked CDDFT PCs, CDDFT encrypted laptops or CDDFT encrypted USB memory sticks.

Patient data were kept secure at all times in accordance with the Data Protection Act and local / national NHS information governance criteria.

Chapter 5. Statistical methodology

In this chapter the types of data that were collected during the Reveal™ and Carelink™ (Real Care) study and the statistical methods used to analyse the primary and secondary outcomes are presented.

5.1. Data types in the Real Care Study

The majority of data collected during the Real Care study was continuous data as it related to the time to an event occurring and the number of ECG recordings made, both manual and automatic. The number of ECG recordings was recorded as both the total number and in the separate categories that the implantable loop recorder (ILR) distinguished, i.e: fast ventricular tachycardia (FVT), ventricular tachycardia (VT), bradycardia (Brady), and asystole (ASY). These numbers were then further stratified as true and false.

5.2. Statistical software

All statistical analysis for the Real Care study was carried out using the Statistical Package for the Social Sciences (SPSS) version 20. This was accessed using the County Durham and Darlington NHS Foundation Trust's (CDDFT's) and Durham University's licences.

5.3. Statistical analysis, exploring the data

All data was explored and assessed using descriptive statistics and plots where appropriate in order to gain an in-depth understanding of the data before hypothesis testing and further testing was carried out. The reason for exploring the data in this way was to highlight anomalies and outliers, and to allow some visualisation of the data prior to analysis.

5.4. Statistical analysis, testing the primary outcome

The primary outcome measures were related to the time to diagnosis and the time from ECG / event occurrence to follow-up. More specifically, whether a cardiac or non-cardiac diagnosis could be made with a clinically significant reduction in time and whether significant ECG recordings could be followed up more quickly. Due to the distribution of the data from pilot and published studies (44,68) the sample size was calculated to be analysed using the log rank (Kaplan – Meier) test for survival.

The log rank test is commonly used when analysing the 'survival' and hazard ratio of data from this type of intervention comparison clinical trial (70). Most commonly the test is used to try to prove an increase in actual survival or prevention of re-hospitalisation. In this case however survival time is preferable when shorter as this would indicate that either a true event (Table 4 - The Real Care Classification of ILR ECG Recordings) has been identified or that a diagnosis has been reached. As with all tests, there are those that criticise its use, stating that the assumptions that all patients are equal at baseline in terms of health status and any other underlying reason that may cause an event to occur. In most cases however, particularly in medical research these assumptions and possible shortfalls are acceptable as they are unavoidable and by using a randomisation technique the impact of any single interaction is reduced (71).

5.5. Statistical analysis, testing the secondary outcomes

The secondary aims of the Real Care study were to provide information on data review burden of conventional verses remote follow-up, impact of remote

monitoring on device memory saturation, whether age and gender can be used as determinants for diagnosis in the CDDFT ILR population; and to provide information regarding CDDFTs ILR implant rates, diagnostic yield and diagnosis, true and false event triggers, time to first event, implant indications, and response to diagnosis in terms of monitoring strategy. The secondary outcomes were to be calculated and presented using descriptive statistics and compared using statistical testing such as Mann-Whitney U where possible. Cox regression was to be used to see if age and / or gender could be used as determinants that affected the hazard ratio (HR) of a diagnosis being reached.

5.6. Verification of statistical tests

All tests and data were reviewed by the Chief Investigator (CI) and Statistician Dr Douglas Wilson (School of Medicine, Pharmacy and Health, Durham University) to ensure that the appropriate tests were used to analyse the data.

Chapter 6. Results

In this chapter the results of the Reveal™ and Carelink™ (Real Care) study are presented. The chapter starts with a results analysis workflow diagram (section 6.1) and then goes into the analysis and results. Before the analysis begins there is a brief recap of patient numbers in the form of a CONsolidated Standards Of Reporting Trials (CONSORT) Diagram. In brief the order of the analysis is; demographic and descriptive statistics, followed by the primary and secondary outcome data.

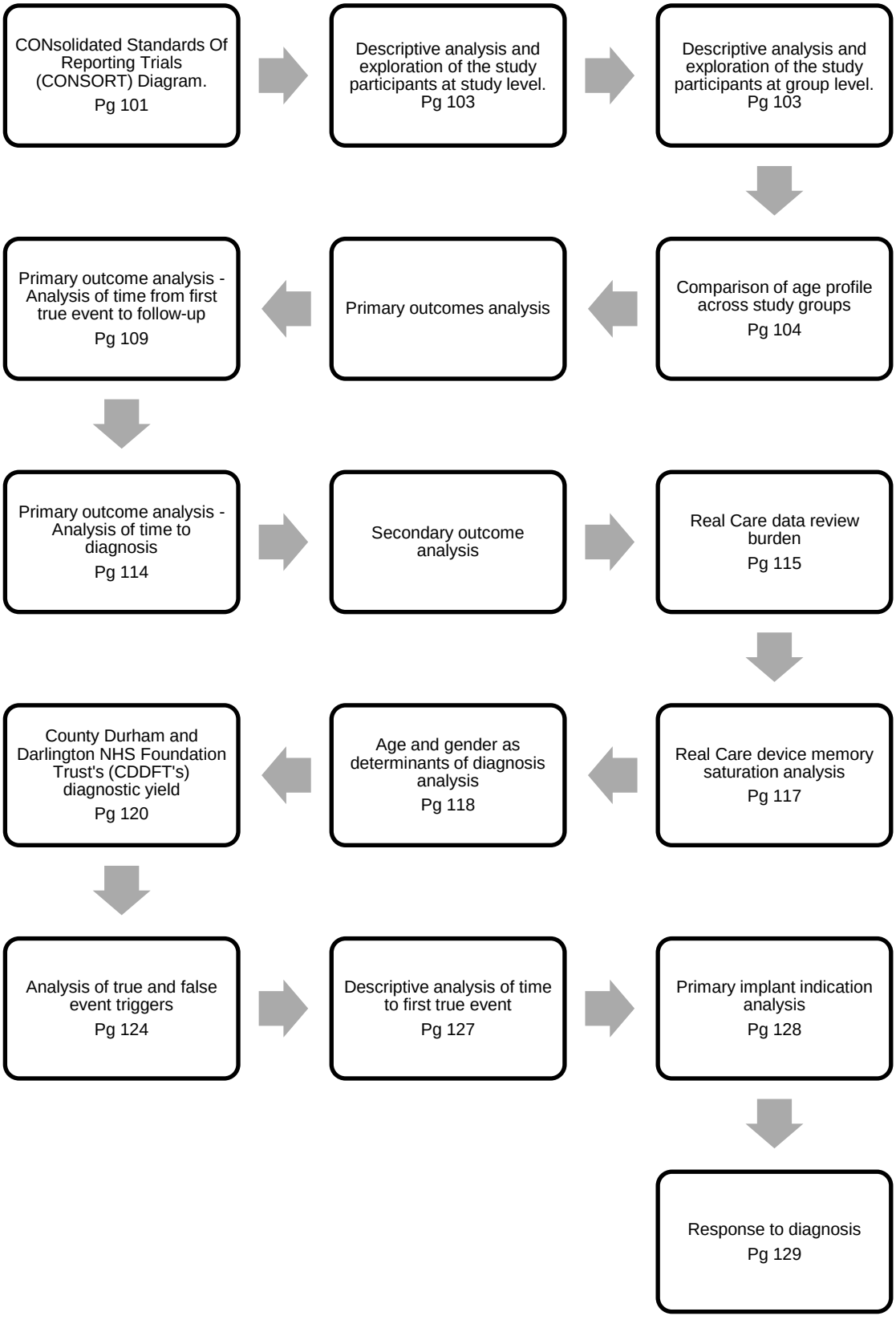
In basic terms the primary outcome analysis aimed to see if:

a) True event ECGs could be picked up more quickly

b) A diagnosis could be reached more quickly

It is important to clarify that there is a difference between a true event ECG and a diagnosis. True events are classified in Table 4 - The Real Care Classification of ILR ECG Recordings on page 85. A single true event may be classed as not being clinically significant in some cases. However, a diagnosis means that a cardiac cause for the patient's symptoms can be ruled in or ruled out. The term diagnosis is therefore used throughout this thesis with the terms 'cardiac' or 'non-cardiac'.

6.1. Results analysis workflow

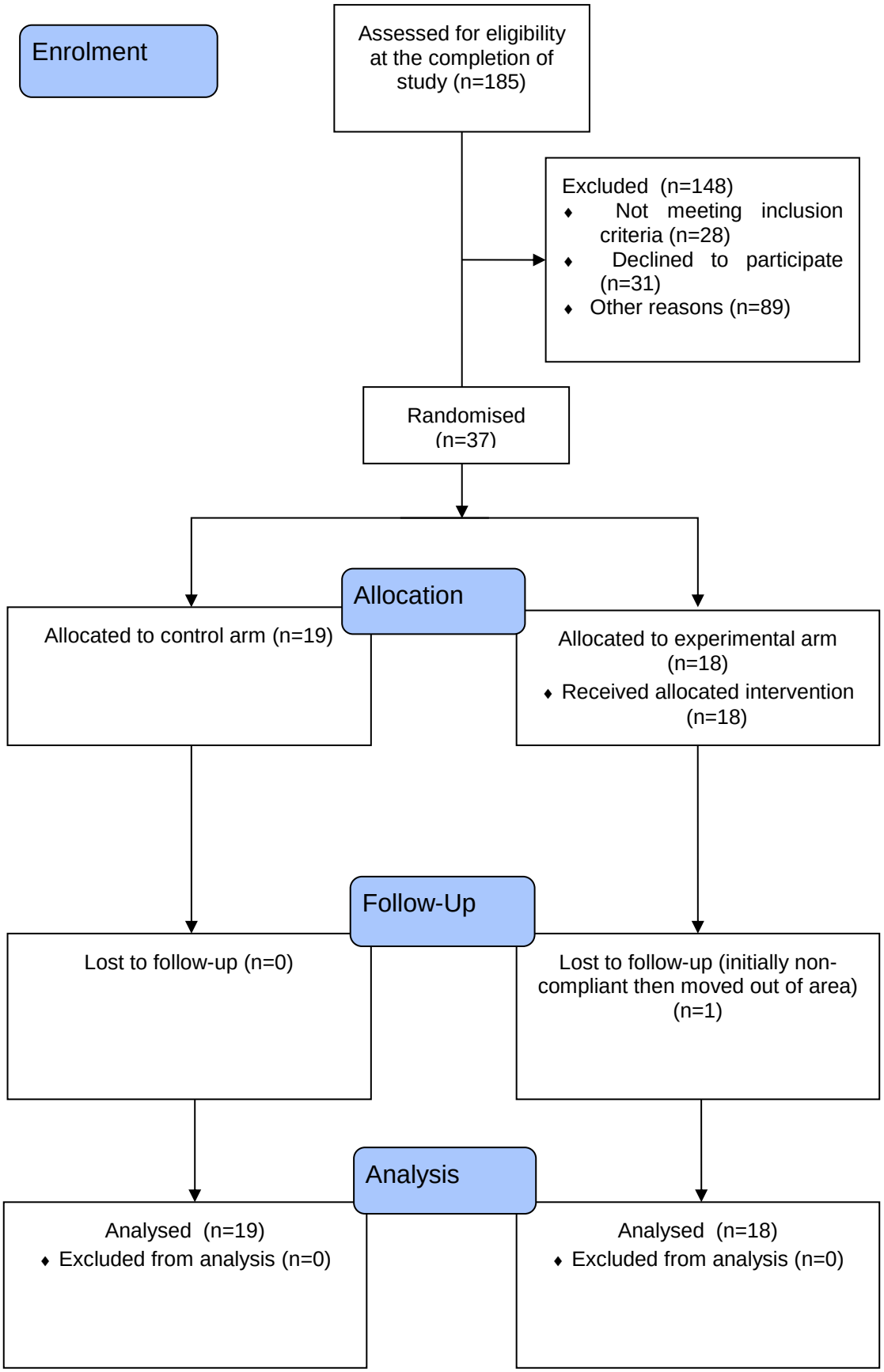


6.2. CONsolidated Standards Of Reporting Trials (CONSORT) diagram for the Real Care study

The CONSORT diagram was created by the CONSORT group to be used alongside the CONSORT statement. The CONSORT group is made up of experts in clinical trial methodology and guideline development as well as journal editors and research funders. CONSORT was designed to promote transparent and structured reporting of randomised controlled trials (RCTs) (72). The statement was created with RCT reporting in terms of journal articles or funder reports in mind, whilst the statement is helpful and the points are covered within this thesis the suggested structure does not quite fit and therefore only the diagram was used.

The reason for using the diagram is to provide a quick overview of how many patients were assessed, enrolled, excluded, randomised, allocated to each group, lost to follow-up, and finally analysed. The CONSORT diagram can be found in Figure 15.

Figure 15 - CONSORT diagram



6.3. Descriptive analysis and exploration of the study participants

6.3.1. Descriptive analysis and exploration of the study participants at study level

Of the 37 patients available for analysis there were 19 male and 18 female. The mean age of the combined groups was 63 ± 16 years with a median age of 63 (36 – 89) years. Table 5 - Descriptive statistics for participant gender and age shows the age and gender profile of all participants in the Real Care study.

Table 5 - Descriptive statistics for participant gender and age

	No. of Patients	% of total	Mean Age (Years)	Std. Deviation	Median Age (Years)	Minimum Age (Years)	Maximum Age (Years)
Total	37	100	63	16	63	36	89
Female	18	49	63	15	67	36	88
Male	19	51	62	17	60	36	89

The mean age breakdown for gender was 63 ± 15 years and 62 ± 17 years for female and male respectively. The median age breakdown by gender was 67 (36 - 88) years for female participants and 60 (36 - 89) years for male participants.

6.3.2. Descriptive analysis and exploration of the study participants at group level

The 18 patients in the experimental (Carelink™) arm were made up of ten males and eight females. The mean age of the group was 59 ± 15 years with the female / male breakdown being 57 ± 13 years / 62 ± 18 years respectively.

The median age for the group was 58 (36 – 84) years, female 66 (37 – 86) years, male 68 (36 – 89) years (Table 6).

The 19 patients in the control (conventional care) arm were made up of 11 males and eight females. The mean age of the group was 65 ± 16 years with the female / male breakdown being 70 ± 14 years / 63 ± 17 years respectively. The median age for the group was 60 (36 – 86) years, female 74 (45 – 88) years, male 68 (36 – 89) years (Table 6).

Table 6 - Descriptive statistics for age and gender breakdown for Real Care participants by study group shows the age and gender breakdown for Real Care participants when stratified by study group.

Table 6 - Descriptive statistics for age and gender breakdown for Real Care participants by study group

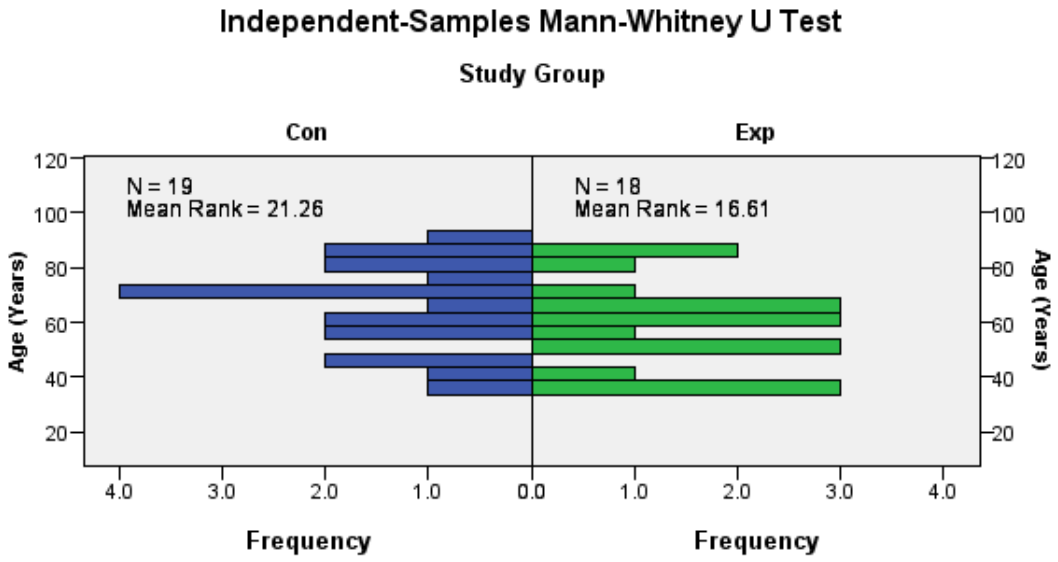
Study Group		No. of Patients	Mean Age (Years)	Std. Deviation	Median Age (Years)	Min Age (Years)	Max Age (Years)
Exp	Female	10	57	13	59	36	84
	Male	8	62	18	66	37	86
	Group Total	18	59	15	60	36	86
Con	Female	8	70	14	74	45	88
	Male	11	63	17	68	36	89
	Group Total	19	66	16	69	36	89

6.3.3. Comparison of age profile across study groups

The Mann-Whitney U test carried out on distribution of age showed that there was no significant difference in the age profiles across the two study groups. The output showing the tests carried out by SPSS as part of the Mann-

Whitney U comparison can be seen in Figure 16 - Mann-Whitney U test comparing age distribution across the study groups.

Figure 16 - Mann-Whitney U test comparing age distribution across the study groups



Total N	37
Mann-Whitney U	214.000
Wilcoxon W	404.000
Test Statistic	214.000
Standard Error	32.893
Standardized Test Statistic	1.307
Asymptotic Sig. (2-sided test)	.191
Exact Sig. (2-sided test)	.199

6.4. Primary outcome analysis

The time taken to reach a diagnosis for ILR patients can be prolonged due to a variety of reasons already covered in this thesis. Essentially the Real Care study was designed to determine whether the use of remote monitoring in conjunction with ILRs is a practical means of reducing the time taken to achieve a diagnosis, or reducing the time taken to discover potentially diagnostic ECG recordings.

In short, statistically the answer to both of these questions is yes. The results of the statistical tests carried out for the analysis that derived the answer to the basic questions are presented in this section.

In order to assess the differences in time from true event ECG to follow-up, the Mann-Whitney U test was used initially to confirm a significant difference, advanced analysis was then carried out using survival testing. Survival testing commonly referred to as time to event (TTE) testing can be defined as a method group for analysing data where the desired outcome is time to occurrence of an event e.g. time to discovery / follow-up of a true event ECG, or time to diagnosis. The time to a defined binary event or survival time can be measured in days, weeks, years, etc from an unambiguous onset of a specific follow-up period (e.g. date of randomisation) until its end e.g. 2 years. There are some important features of TTE analysis some of which are right-censored in nature (the true unobserved event is to the right of the censoring time); i.e., all that is known is that the event has not happened during follow-up and not that an event will not occur. In simple terms the right censoring occurs when the event of interest did not occur in the follow-up period, or if

the participant left the study before the event had occurred. The censoring time is the time at which either the patient left the study or the study ended without the event of interest occurring. This often happens when a study uses staggered entry (as in the Real Care study) - 'patients' do not all enter the study at the same time; patients may not have experienced the event at the time when the study ends (right-censored at study termination); or else patients have dropped out (right-censored at drop-out) and the last time they were monitored the event had not occurred; some patients become lost in the middle of the study (right censored-lost to follow-up), and the last time they were monitored they were event-free. In the case of right-censoring where the study is designed to end after a pre-set time but patients do not have the same censoring time, this is referred to as 'random type 1 right-censoring' which is the most common form of right censoring. If there was no censoring, and subject to appropriate transformation of the time to event, linear regression analysis could be used. However, TTE analysis is more appropriate because time to event has a skewed distribution; the probability of being event-free past a certain time point may be of more interest than the expected time of event; and the hazard function used in TTE can lead to greater insight into significant failure factors that may be of clinical interest.

For analysis of the Real Care data Kaplan-Meier was the advanced analysis tool used within the Statistical Package for the Social Sciences (SPSS) as it uses exact times events occur rather than the interval times used in other forms of survival analysis. The use of exact event times over interval times makes Kaplan-Meier analysis more appropriate for this trial data and a significant advantage since the cumulative probability of having an event is for

that time point which takes on the value of the previous time point: consequently the TTE graph takes the form of a step function (and it is incorrect to join points other than by slopes of zero), a drop in value occurring only when an event occurs. It uses all available information and is useful for trial data of small sample sizes: censored times can be annotated on each event-free graph. For each time interval, t, the survival probability is calculated as the number of subjects surviving (number of patients living at the start of the time (e.g. 2 months minus the number of events) divided by the number of patients at risk (all living at the start) and those who are censored are not included in the denominator. Total probability of event-free occurrence up to that time interval is obtained by multiplying all the probabilities of being syncope-free at all time intervals preceding that time (i.e. by applying law of multiplication of probability to calculate cumulative probability). For example, the probability of patients being syncope-free three months after randomisation can be considered to be the probability of being syncope-free after two months multiplied by the probability of being syncope-free in the third month. This second probability is called a conditional probability. Although the probability calculated at any given time interval (i.e. every three months) is not very accurate because of the small number of events, the overall probability of being event-free at each specific time point is more accurate.

Formally, the Kaplan-Meier estimate of remaining event-free is given by *k* patients having events in the period of follow-up at distinct times $t_1<t_2<t_3<t_4<t_5<\cdots<t_k$. The probability of being event-free at time t_j, $S(t_j)$, is

calculated from $S(t_{j-1})$ the probability of being alive at t_{j-1}, n_j is the number of patients alive just before t_j, and d_j the number of events at t_j, by

$$S(t_j) = S(t_{j-1})\left(1 - \frac{d_j}{n_j}\right)$$

Furthermore SPSS uses the Log-rank test as part of the Kaplan-Meier analysis to compare event free probabilities and demonstrate the significance of any observed changes between groups.

6.4.1. Analysis of time from true event to follow-up

Moving on to the first set of primary outcome data, the median time from first true event ECG to follow-up in the combined group data was 2 (0 – 24) weeks. The median time from first true event ECG to follow-up in the experimental group data was one (zero – five) week and the median time from first true event ECG to follow-up in the control group was three (zero – 24) weeks. The median, minimum, and maximum figures can be seen in Table 7 - Descriptive statistics for Real Care time from true event to follow-up, complete and split by group.

Table 7 - Descriptive statistics for Real Care time from true event to follow-up, complete and split by group

Combined	N=	28
	Median (Weeks)	2
	Minimum (Weeks)	0
	Maximum (Weeks)	24
Exp	N=	13
	Median (Weeks)	1
	Minimum (Weeks)	0
	Maximum (Weeks)	5
Con	N=	15
	Median (Weeks)	3
	Minimum (Weeks)	0
	Maximum (Weeks)	24

The Mann-Whitney U test outputs (Figure 17 and Figure 18) highlight that there was a statistically significant difference between the median times for a true event to be discovered at a follow-up between groups.

Figure 17 - Test of median time from true event to follow-up

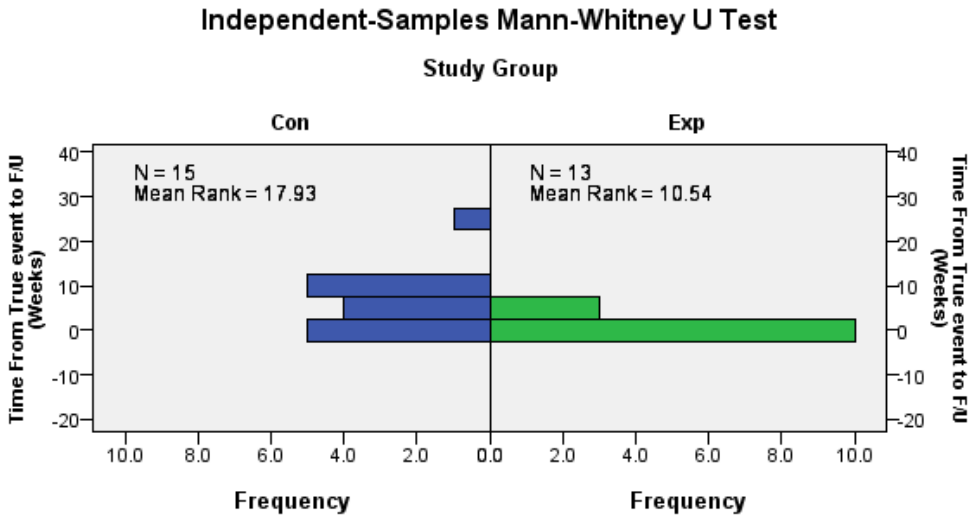
Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Time From True event to F/U (Weeks) is the same across categories of Study Group.	Independent-Samples Mann-Whitney U Test	.017[1]	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

[1]Exact significance is displayed for this test.

Figure 18 - Mann-Whitney U test comparison illustration and test statistics used in the calculation



Total N	28
Mann-Whitney U	149.000
Wilcoxon W	269.000
Test Statistic	149.000
Standard Error	21.433
Standardized Test Statistic	2.403
Asymptotic Sig. (2-sided test)	.016
Exact Sig. (2-sided test)	.017

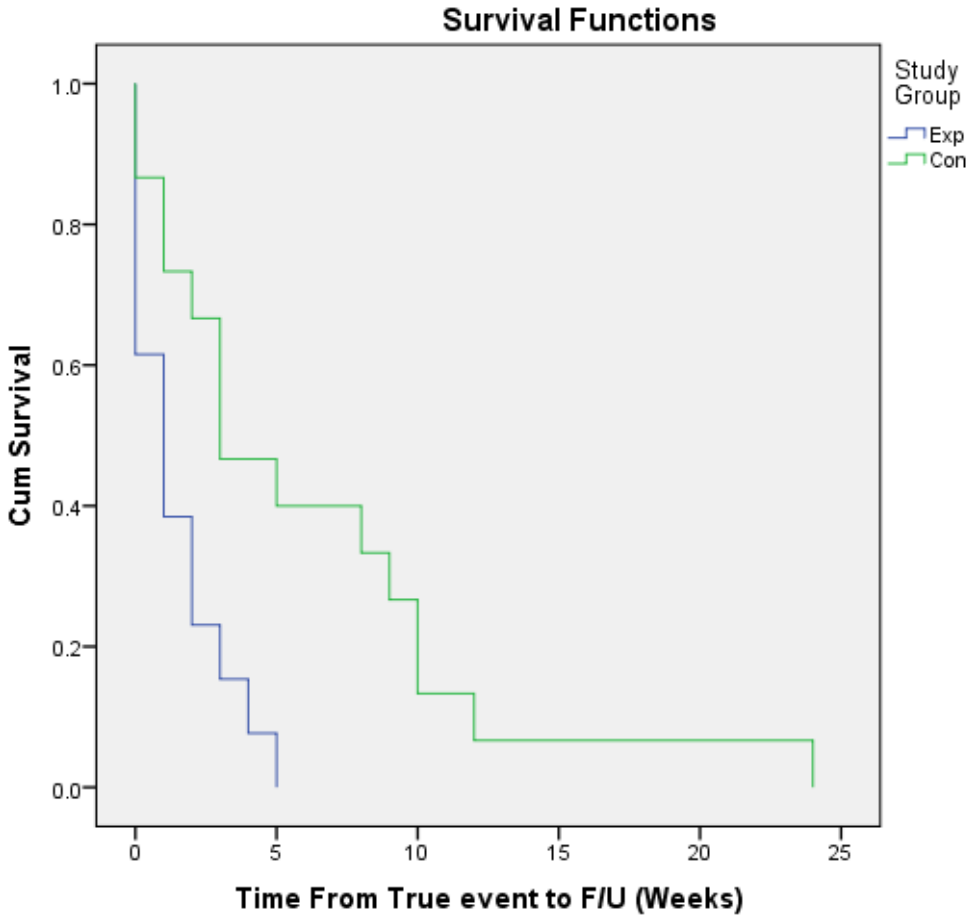
The analysis results seen in Table 8 - Median survival for time from a true event to follow-up shows that 50% of patients that have a true event ECG in the control group will have had to wait an estimated three weeks until they were followed-up, whereas 50% of the patients in the experimental group are estimated to have had their follow-up one week after a true event occurred.

Table 8 - Median survival for time from a true event to follow-up

Study Group	Median (Weeks)			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Exp	1.000	.585	.000	2.674
Con	3.000	1.449	1.790	4.210
Overall	2.000	.754	.577	3.423

The survival plot in Figure 19 - Survival plot for time from true event to follow-up shows that the survival probability of experimental group patients having to wait for their true event to be followed-up is lower at all time points. It is worthwhile noting at this point that “survival” is not the primary outcome of this study and that the endpoints depicted in the survival plots are those of true event occurrence and diagnosis.

Figure 19 - Survival plot for time from true event to follow-up



The log-rank test showed that there is a statistically significant difference (p = 0.004) between the time taken from a true event occurring and the subsequent follow-up depending on the mode of follow-up. The results of the log-rank test can be seen in Table 9 - Log-rank test results for time from true event ECG to follow-up

Table 9 - Log-rank test results for time from true event ECG to follow-up

	Chi - Square	df	Sig.
Log Rank (Mantel – Cox)	8.105	1	.004

6.4.2. Analysis of time to diagnosis

The primary outcome of diagnostic time difference is shown in the survival plot, and the log rank test table in Figure 20, Table 10 and Table 11.

Table 10 - Median time to diagnosis by study group

Study Group	Median (Weeks)			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Exp	6.000	2.372	1.351	10.649
Con	13.140	3.853	5.589	20.691
Overall	10.000	.799	8.435	11.565

Figure 20 - Survival plot for time to diagnosis by study group

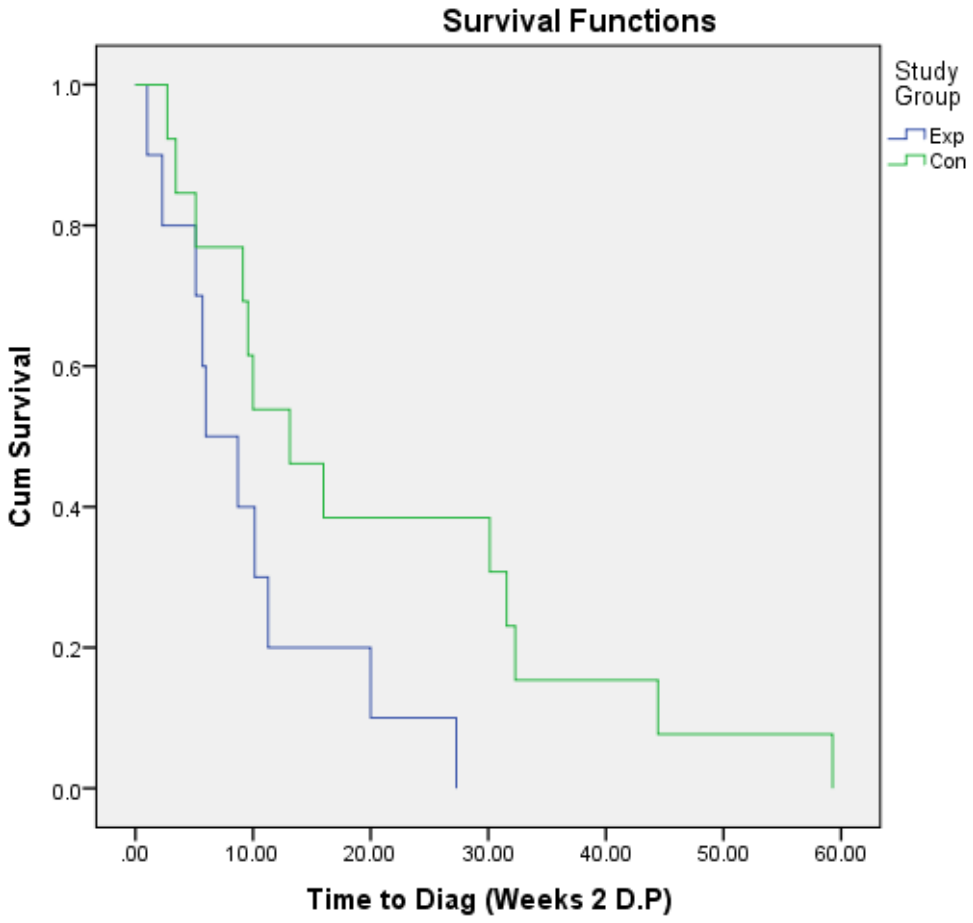


Table 11 - Log-Rank test results for time to diagnosis by study group

	Chi - Square	df	Sig.
Log Rank (Mantel – Cox)	3.889	1	.049

Figure 20 - Survival plot for time to diagnosis by study group shows an early divergence in time to diagnosis between the two groups, with the experimental group clearly receiving a diagnosis more quickly. However this is only of borderline statistical significance as demonstrated by the Log-Rank test with P = 0.49. Further discussion of this and the relationship between statistically significant and clinically significant findings is covered in Chapter 7.

6.5. Secondary outcome analysis

6.5.1. Real Care data review burden

In total the Real Care study produced data from 5526 event recordings (total of automated and manual recordings, with and without ECG) for review in the analysis. It is worth mentioning again at this point that the Reveal™ ILR can only hold 49.5 minutes of recording at any one time, if the memory is full then the oldest recording will be overwritten and the details of the event held as a text event. The text includes time and date of event, duration of event, heart rate (min, max, and average) along with the device classification of the event. Whilst not as informative or potentially diagnostic as the ECG recordings, text events still require review particularly in patients with symptoms corresponding to the time of an event without ECG. Text events are also important when looking at the duration of an arrhythmia, for example if a tachycardia rate is only just at the detection rate programmed in the ILR or

dips out of the detection zone slightly then enters the detection zone again, the device would record each dip as a separate event. This would show as lots of recordings over the same time period when in fact it was a single sustained episode lasting from the first text recording to the last recording with ECG. The 5526 events equated to 1711 ECG recordings requiring review and 3815 text events (without ECG) recordings. (Recordings with ECG are between one minute and seven and a half minutes in length depending on whether the recording is automated or manual). When breaking down the 5526 event recordings into recordings per study group there were 1264 events logged for the control group, 481 with ECGs and 783 without ECG to review and 4262 events logged for the experimental group, 1230 with ECGs and 3032 without ECG to review.

On further investigating the 5526 events recorded. The breakdown of these events was as follows. In the experimental group 4262 recordings were logged, 1230 of those recordings had ECGs to analyse. The breakdown of the recordings was 200 FVTs, 132 VTs, 216 asystoles, 2799 bradycardias, 836 AT/AF, and 79 manual recordings. Of the 1230 ECG recordings, 153 (12%) were true events for this cohort. There were 1264 recordings logged in the control group data with 481 ECGs to analyse. The breakdown of this was 206 FVTs, 22 VTs, 74 asystoles, 285 bradycardias, 527 AT/AF, and 150 manual recordings. Of the 481 ECG recordings, 122 (25%) were true events for this cohort.

6.5.2. Real Care device memory saturation analysis

The mean device memory saturation was 18% and 25% for the experimental and control groups respectively. There was no significant difference in the percentage of device memory saturation, regardless of whether follow-up mode was remote or conventional. The results can be seen in Table 12 - Descriptive statistics for device memory saturation and Figure 21 - Device memory saturation Mann -Whitney U test results.

Table 12 - Descriptive statistics for device memory saturation

Saturation %

Exp	N=	17
	Mean	18
	Std. Deviation	30
	Minimum	0
	Maximum	99
Con	N=	19
	Mean	25
	Std. Deviation	35
	Minimum	0
	Maximum	95

Figure 21 - Device memory saturation Mann -Whitney U test results

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Saturation % is the same across categories of Study Group.	Independent-Samples Mann-Whitney U Test	.778[1]	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

[1]Exact significance is displayed for this test.

6.5.3. Age and gender as determinants of diagnosis analysis

When performing Cox regression on the data from the Real Care study, using the variables, study group, age group in years (30-50, 51-70, 71 and over), and gender the test showed that when controlling for age group and gender the "risk" of diagnosis in the experimental group was 2.7 times higher than that of patients in the control group (HR = 2.709, p = 0.049). Neither of the other variables (age and gender) were statistically significant. It is worth noting however that if the age group variable was introduced as a categorical variable the hazard ratio (HR) was increased. By introducing the variable this way, rather than controlling for just the average of each age group it also compares each age group against a 'baseline group' in this case the 30 – 50 year old group. The increase suggests that patients in the experimental group have a "risk" or chance just over three times that of the control patients of receiving a diagnosis (HR = 3.128, p = 0.028). Table 13 and Table 14 show the results of the regression analysis. Unfortunately, the study was not powered to assess HR and with larger group sizes the effect of the variables included could be altered. Therefore these results may require caution in their interpretation and transference as the possibility of a chance finding cannot be overlooked.

Table 13 - Cox regression for study group, age group, and gender

Variable	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
StudyGroup	.997	.497	4.027	1	.045	2.709	1.023	7.172
AgeGroup2	-.169	.293	.335	1	.563	.844	.476	1.498
Gender	.615	.445	1.909	1	.167	1.850	.773	4.428

(AgeGroup2 (years) 30-50, 51-70, 71 and over. N.B.SPSS uses group means in calculations)

Table 14 - Cox regression for study group, age group, and gender with age group as a categorical covariate

Variable	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
StudyGroup	1.140	.518	4.840	1	.028	3.128	1.133	8.638
AgeGroup2			1.786	2	.409			
AgeGroup2(1)	.411	.567	.526	1	.468	1.509	.497	4.584
AgeGroup2(2)	-.375	.646	.337	1	.561	.687	.194	2.436
Gender	.810	.483	2.806	1	.094	2.248	.871	5.797

(AgeGroup2 = 30-50 years, AgeGroup2(1) = 51-70 years, AgeGroup2(2) = 71 and over)

The original age groups were not suitable for the Cox regression analysis and therefore required updating. This update reduced the data from five age categories down to three age categories (the original age grouping was 30-40, 41-50, 51-60, 61-70, and 71 and over). The rationale behind this update was to increase the numbers within the outlying categories and minimise the skew effect and interaction that occurred in the first Cox regression analysis attempt. Table 15 and Table 16 show the initial Cox regression findings. The influence of having five age categories, some of which had only four patients and were 75% male is clearly seen in Table 16.

Table 15 - Cox regression for study group and age group (Initial age group categories)

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
StudyGroup	.621	.297	4.363	1	.037	1.861	1.039	3.334
AgeGroup			1.671	4	.796			
AgeGroup(1)	.850	1.162	.536	1	.464	2.340	.240	22.800
AgeGroup(2)	.466	.683	.466	1	.495	1.594	.418	6.082
AgeGroup(3)	.476	.647	.541	1	.462	1.609	.453	5.721
AgeGroup(4)	.931	.774	1.448	1	.229	2.538	.557	11.567

(AgeGroup = 30-40, AgeGroup(1) = 41-50, AgeGroup(2) = 51-60, AgeGroup(3) = 61-70, AgeGroup(4) = 71 and over)

Table 16 - Cox regression analysis on study group, age group and gender (Initial age group categories)

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
StudyGroup	.652	.299	4.742	1	.029	1.918	1.067	3.448
AgeGroup			3.395	4	.494			
AgeGroup(1)	1.484	1.246	1.417	1	.234	4.410	.383	50.750
AgeGroup(2)	.204	.675	.091	1	.763	1.226	.327	4.600
AgeGroup(3)	.601	.658	.835	1	.361	1.825	.502	6.626
AgeGroup(4)	1.214	.768	2.500	1	.114	3.367	.748	15.164
Gender	.502	.256	3.843	1	.050	1.652	1.000	2.729

(AgeGroup = 30-40, AgeGroup(1) = 41-50, AgeGroup(2) = 51-60, AgeGroup(3) = 61-70, AgeGroup(4) = 71 and over)

6.5.4. County Durham and Darlington NHS Foundation Trust's (CDDFT's) diagnostic yield

On analysis 28 (76%) of the 37 patients had a true event as classified in Table 4 - The Real Care Classification of ILR ECG Recordings on page 85. Table 17 shows the frequency and percentages of participants that recorded a true event ECG.

As previously mentioned in the introduction to this chapter (page 99), there is a difference between a true event ECG and a diagnosis. True events are classified in Table 4 - The Real Care Classification of ILR ECG Recordings on page 85. A single true event may be classed as not being clinically significant in some cases. However, a diagnosis means that a cardiac cause for the patient's symptoms can be ruled in or ruled out. However, as true events lead to diagnosis the analysis of them is included in the diagnostic yield section.

Table 17 - Descriptive statistics for Real Care true event ECG frequencies

True Event	No. of Patients	% of Total
Yes	28	76
No	9	24
Total	37	100

In Total 23 (62%) of the 37 patients received a diagnosis, and of those that received a diagnosis 15 (65%) received a cardiac diagnosis. Table 18 - Descriptive statistics for Real Care diagnosis breakdown shows the frequency and percentages of participants in the Real Care data that received a diagnosis. The diagnosis is then broken down further into cardiac and non-cardiac where 'Yes' = cardiac diagnosis and 'No' = non-cardiac diagnosis in Table 19 - Descriptive statistics showing the breakdown of diagnosis into cardiac diagnosis.

Table 18 - Descriptive statistics for Real Care diagnosis breakdown

Diagnosis	No. of Patients	% of Total
Yes	23	62
No	14	38
Total	37	100

Table 19 - Descriptive statistics showing the breakdown of diagnosis into cardiac diagnosis

		No. of Patients	% of Total	Valid %
Cardiac Diagnosis	Yes	15	41	65
	No	8	22	34
	Total	23	62	100
No Diagnosis		14	38	-
Total		37	100	-

When broken down into study group the data showed that 13 (72%) of the 18 patients in the experimental group had a true event (Table 20) and that 10 (56%) received a diagnosis (Table 21). The data for the control group showed that 15 (79%) of the 19 patients had a true event (Table 20) and 13 (68%) of the group's patients received a diagnosis (Table 21). The SPSS outputs of event and diagnosis breakdowns are shown in Table 20 - Breakdown of true event frequencies split by study group and Table 21 - Breakdown of diagnosis frequencies split by study group. In addition to the patients receiving a diagnosis one further patient reached a study endpoint due to device removal. The device was removed at the patients request due to pain at the implant site.

Table 20 - Breakdown of true event frequencies split by study group

			No. of Patients	% of Total
Experimental Group	True Event	Yes	13	72
		No	5	27
		Total	18	100
Control Group	True Event	Yes	15	79
		No	4	21
		Total	19	100

Table 21 - Breakdown of diagnosis frequencies split by study group

	Diagnosis	No. of Patients	% of Total
Experimental Group	Yes	10	56
	No	8	44
	Total	18	100
Control Group	Yes	13	68
	No	6	32
	Total	19	100

Table 22 - Cardiac diagnosis breakdown, split by study group shows that of the ten patients in the experimental group that received a diagnosis, six (60%) received a cardiac diagnosis and four (40%) received a non-cardiac diagnosis. In the control group data, of the 13 patients that received a diagnosis, nine (69%) received a cardiac diagnosis and four (31%) received a non-cardiac diagnosis.

Table 22 - Cardiac diagnosis breakdown, split by study group

	Cardiac Diagnosis	No. of Patients	% of Total
Experimental Group	Yes	6	60
	No	4	40
	Total	10	100
Control Group	Yes	9	69
	No	4	31
	Total	13	100

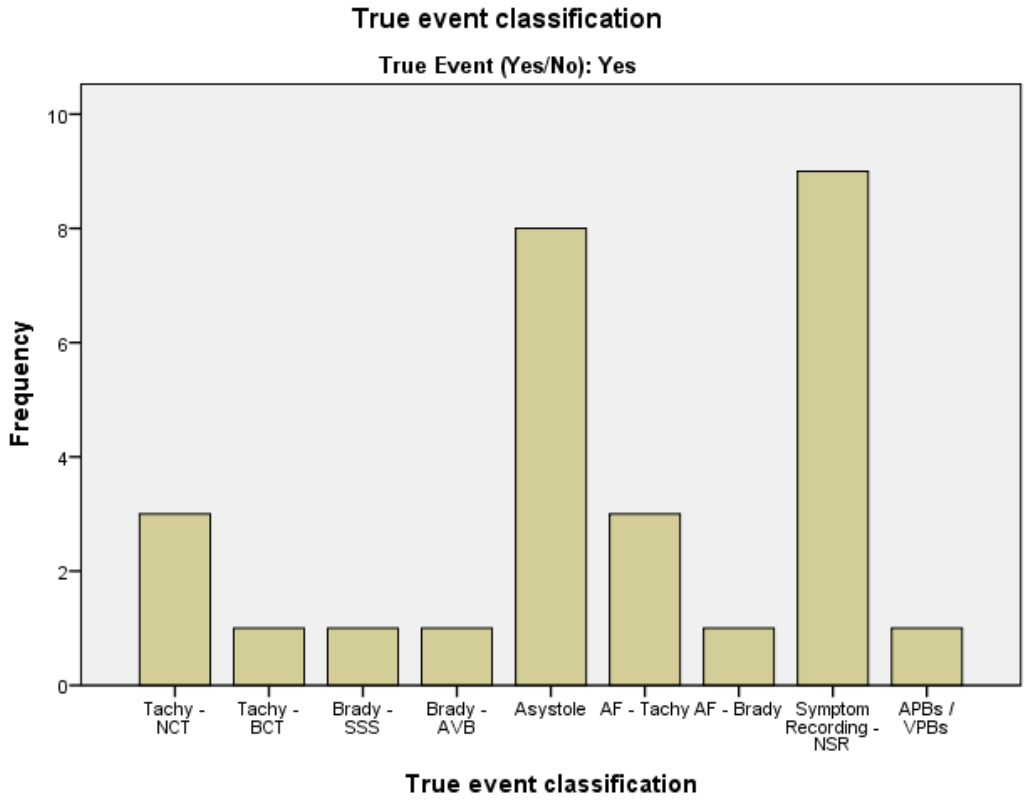
6.5.5. Analysis of true and false event triggers

Table 23 - Real Care true event occurrences and Figure 22 - Real Care true event occurrence chart show the true event types found in the Real Care data. Table 25 - True events and diagnosis breakdown and Figure 24 - Event type leading to diagnosis bar chart then show the breakdown of true events that led to a diagnosis in the Real Care study

Table 23 - Real Care true event occurrences

Event Type	Frequency	% of Total
Tachy - NCT	3	10.7
Tachy - BCT	1	3.6
Brady - SSS	1	3.6
Brady - AVB	1	3.6
Asystole	8	28.6
AF - Tachy	3	10.7
AF - Brady	1	3.6
Symptom Recording - NSR	9	32.1
APBs / VPBs	1	3.6
Total	28	100.0

Figure 22 - Real Care true event occurrence chart



False events were predominantly caused by artefacts with 12 (32%) patients having an artefactual recording. The full breakdown of false events is shown in Table 24 and Figure 23

Table 24 - Real Care false event recording frequency

False Event Type	Frequency	% of Total
No false event	8	21.6
Artefact	12	32.4
Undersensing	6	16.2
Inappropriate activator use	7	18.9
Sinus tachycardia	3	8.1
Brief pause in AF <4.5sec	1	2.7
Total	37	100.0

Figure 23 - Real care false event frequency chart

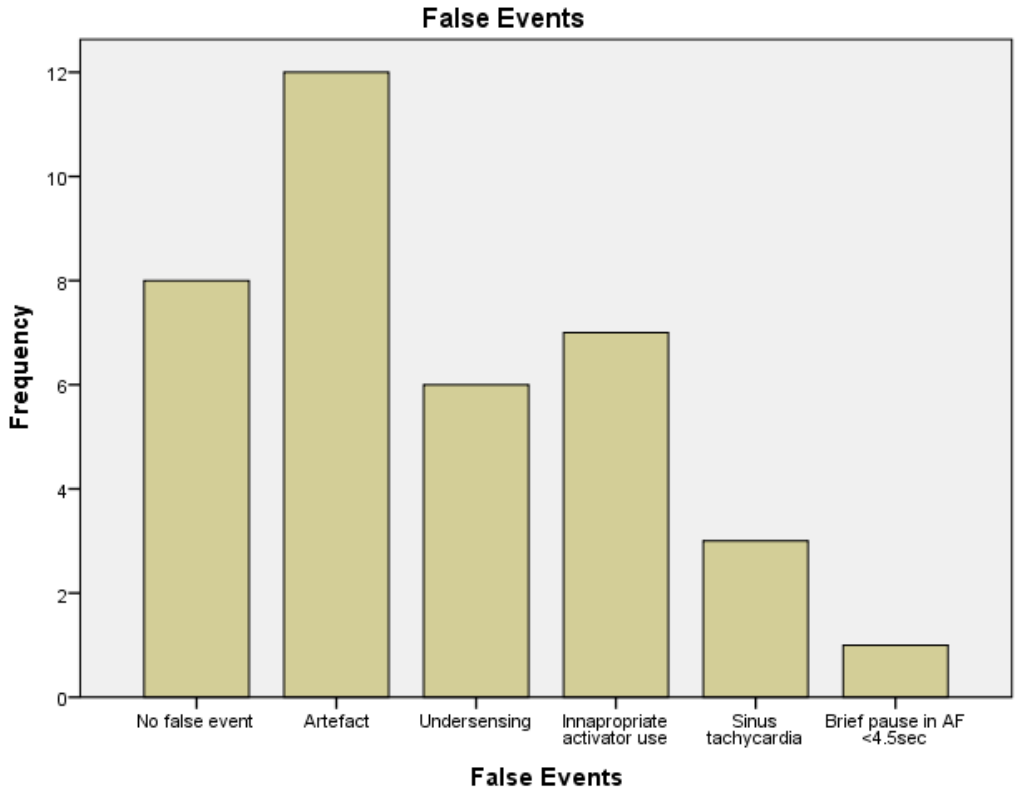
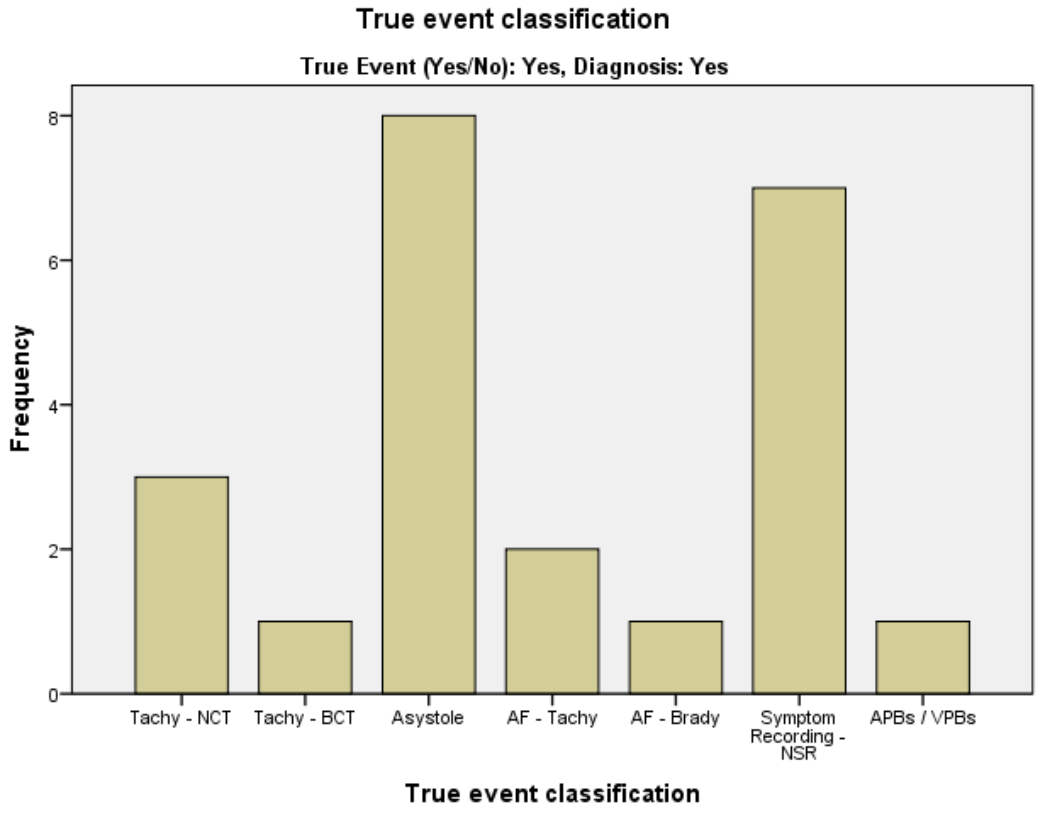


Table 25 - True events and diagnosis breakdown

True Event (Yes/No)	Diagnosis	Event Type	Frequency	% of Total
Yes	Yes	Tachy - NCT	3	13.0
		Tachy - BCT	1	4.3
		Asystole	8	34.8
		AF - Tachy	2	8.7
		AF - Brady	1	4.3
		Symptom Recording - NSR	7	30.4
		APBs / VPBs	1	4.3
		Total	23	100.0
	No	Brady - SSS	1	20.0
		Brady - AVB	1	20.0
		AF - Tachy	1	20.0
		Symptom Recording - NSR	2	40.0
		Total	5	100.0

Figure 24 - Event type leading to diagnosis bar chart



6.5.6. Descriptive analysis of time to first true event

The median time to the first true event ECG for the complete Real Care data was four (0 – 44) weeks. Table 26 - Descriptive data for time to first true event for Real Care data shows the median, minimum and maximum time to first true event in weeks.

Table 26 - Descriptive data for time to first true event for Real Care data

N =	28
Median (Weeks)	4
Minimum	0
Maximum	44

The median time to the first true event in the experimental group data was four (1 - 11) weeks. The median time to the first true event in the control group

data was five (0 - 44) weeks. The SPSS output showing the median, minimum, and maximum time to first true event ECG can be seen in Table 27 - Time to first true event ECG split by study group.

Table 27 - Time to first true event ECG split by study group

Exp	N=	13
	Median (Weeks)	4
	Minimum (Weeks)	1
	Maximum (Weeks)	11
Con	N=	15
	Median (Weeks)	5
	Minimum (Weeks)	0
	Maximum (Weeks)	44

6.5.7. Primary implant indication analysis

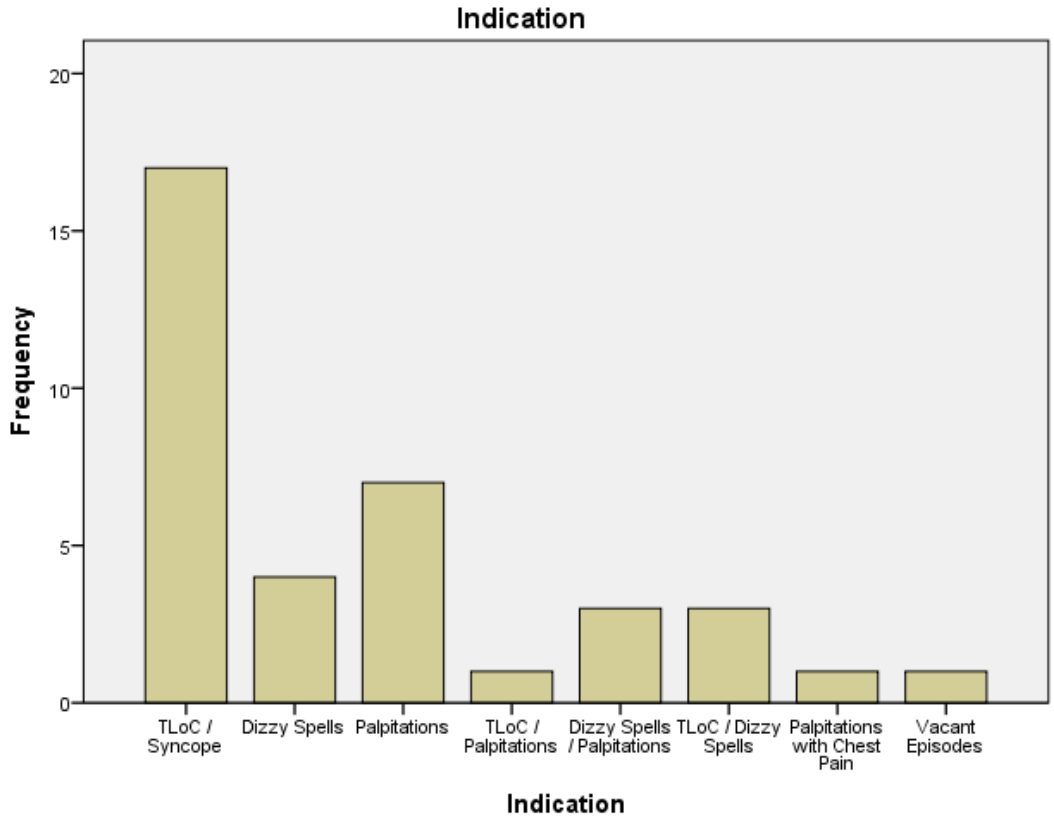
The primary indication for ILR implant in the Real Care data was syncope. Of the 37 patients included in the study, a total of 21 had transient loss of consciousness (TLoC) / syncope as an indication. Ten patients had an indication either solely for, or including dizzy spells. There were 12 patients that had an indication for or including palpitations. Finally one implant was due to vacant episodes. The full breakdown of the implant indications can be seen in Table 28 - Frequency table for implant indication and

Figure 25 - Implant indication bar chart.

Table 28 - Frequency table for implant indication

Indication	Frequency	% of Total
TLoC / Syncope	17	45.9
Dizzy Spells	4	10.8
Palpitations	7	18.9
TLoC / Palpitations	1	2.7
Dizzy Spells / Palpitations	3	8.1
TLoC / Dizzy Spells	3	8.1
Palpitations with Chest Pain	1	2.7
Vacant Episodes	1	2.7
Total	37	100.0

Figure 25 - Implant indication bar chart



6.5.8. Response to diagnosis

The following data illustrates the response in terms of monitoring following a diagnosis. It is worthwhile noting again that a diagnosis can be cardiac or non-cardiac, and that by non-cardiac the inference is that it is unlikely that the

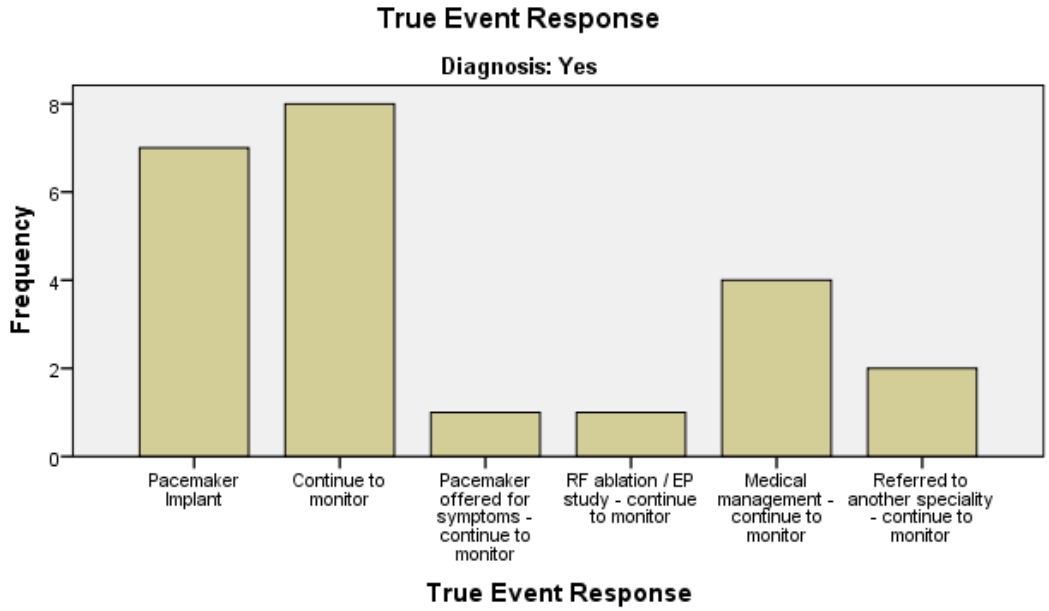
heart is the cause of the implant indication and this does not always mean that a cause has been identified as would be the case in the traditional use of the term ‘diagnosis’. For those that receive a cardiac diagnosis the traditional use of the term ‘diagnosis’ applies. It is also worth mentioning at this point that ILRs are removed when a pacemaker is implanted.

Analysis of the diagnosis data found that 15 (70%) of the patients that received a diagnosis retained their ILR for further monitoring and 7 (30%) patients received a pacemaker.

Table 29 - Frequency table for outcome following diagnosis

Outcome	Frequency	% of Total
Pacemaker Implant	7	30.4
Continue to monitor	8	34.8
Pacemaker offered for symptoms - continue to monitor	1	4.3
RF ablation / EP study - continue to monitor	1	4.3
Medical management - continue to monitor	4	17.4
Referred to another speciality - continue to monitor	2	8.7
Total	23	100.0

Figure 26 - Frequency chart for true event response / outcome following diagnosis



6.6. Example ILR recordings from the Real Care study

The following figures are examples of recordings made by CDDFT ILR patients; the figure titles will state the type and classification of the recording.

Figure 27 - Artefact, false event recorded as FVT

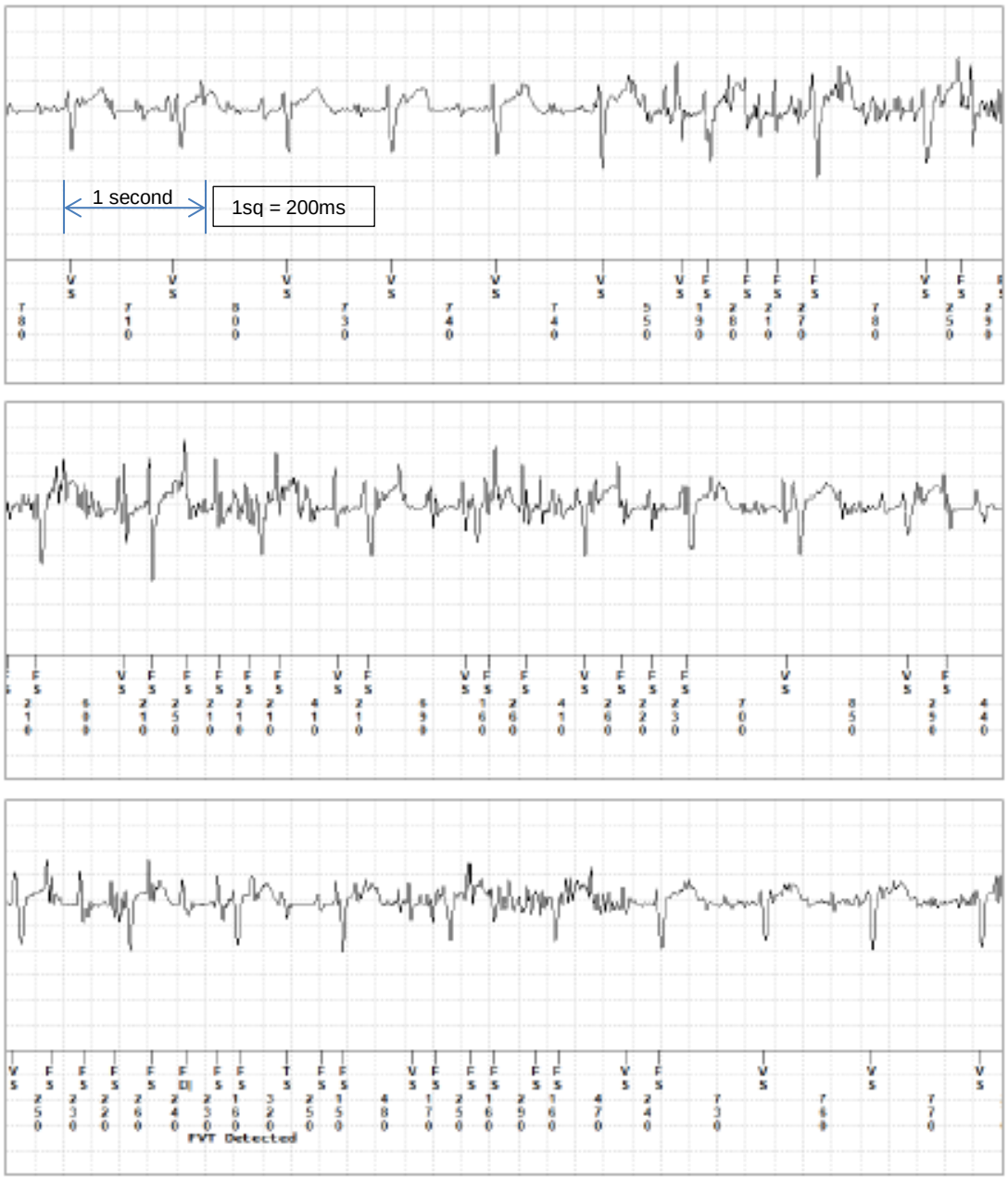


Figure 28 - SVT, true event

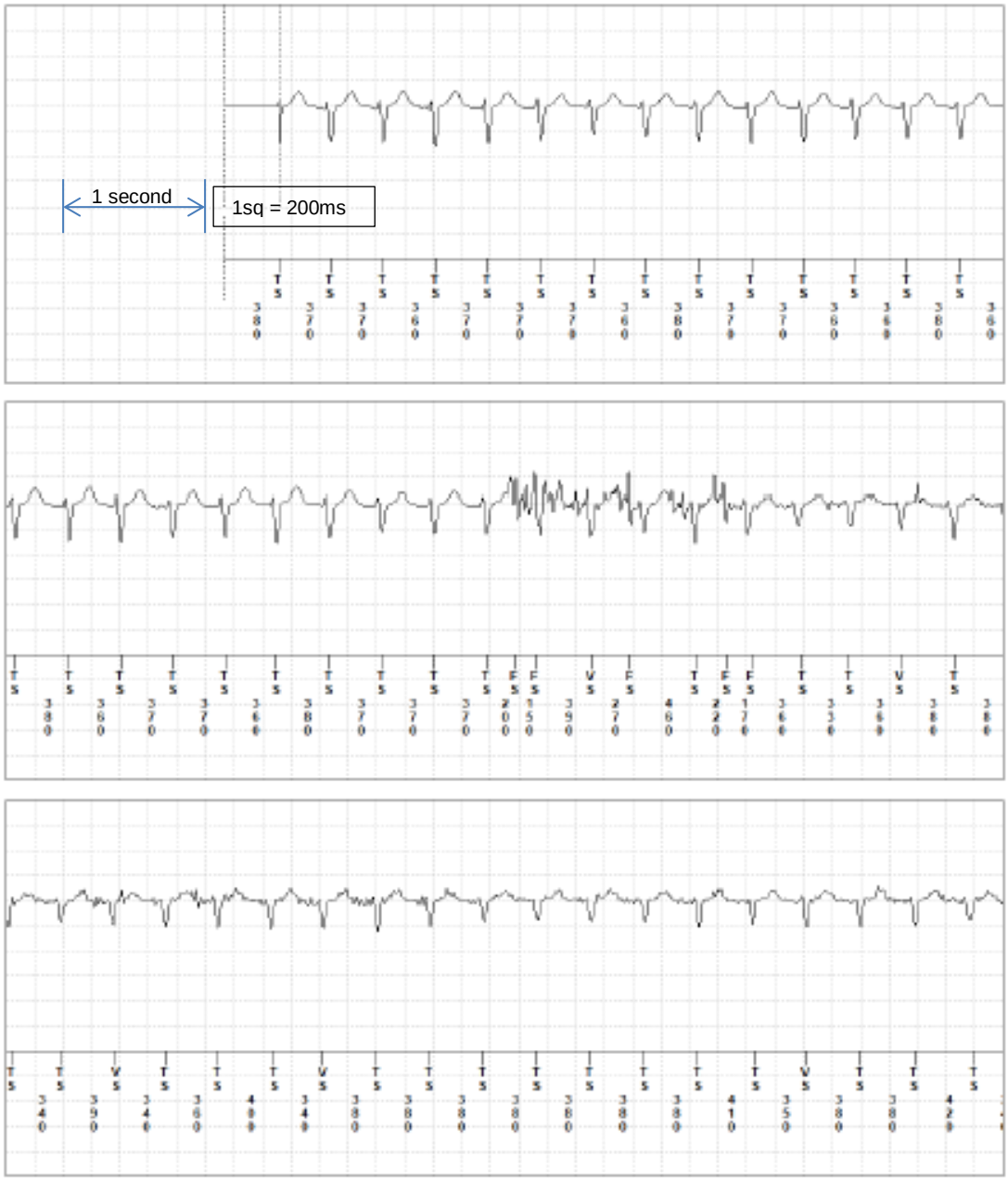


Figure 29 - Sudden bradycardia

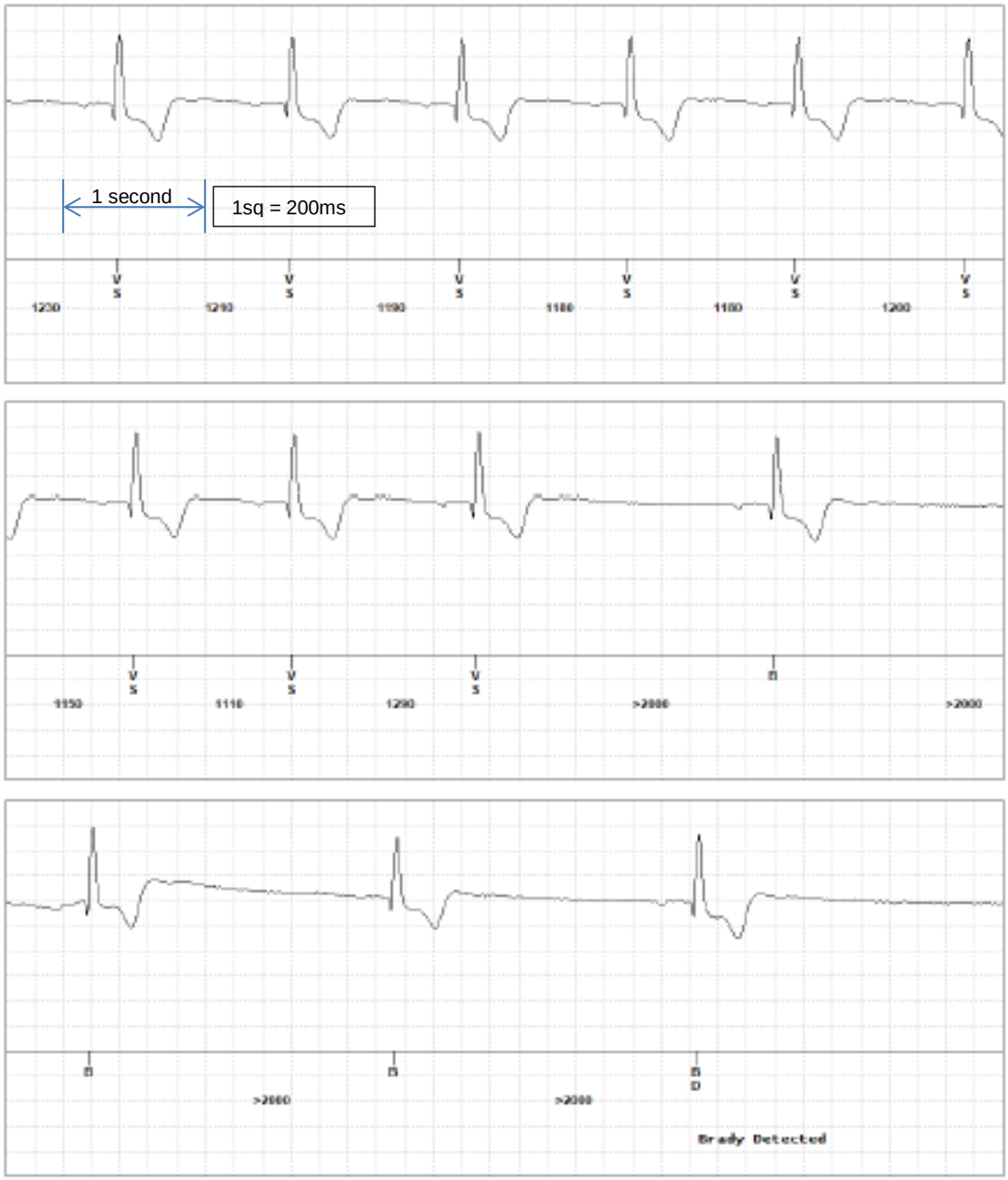
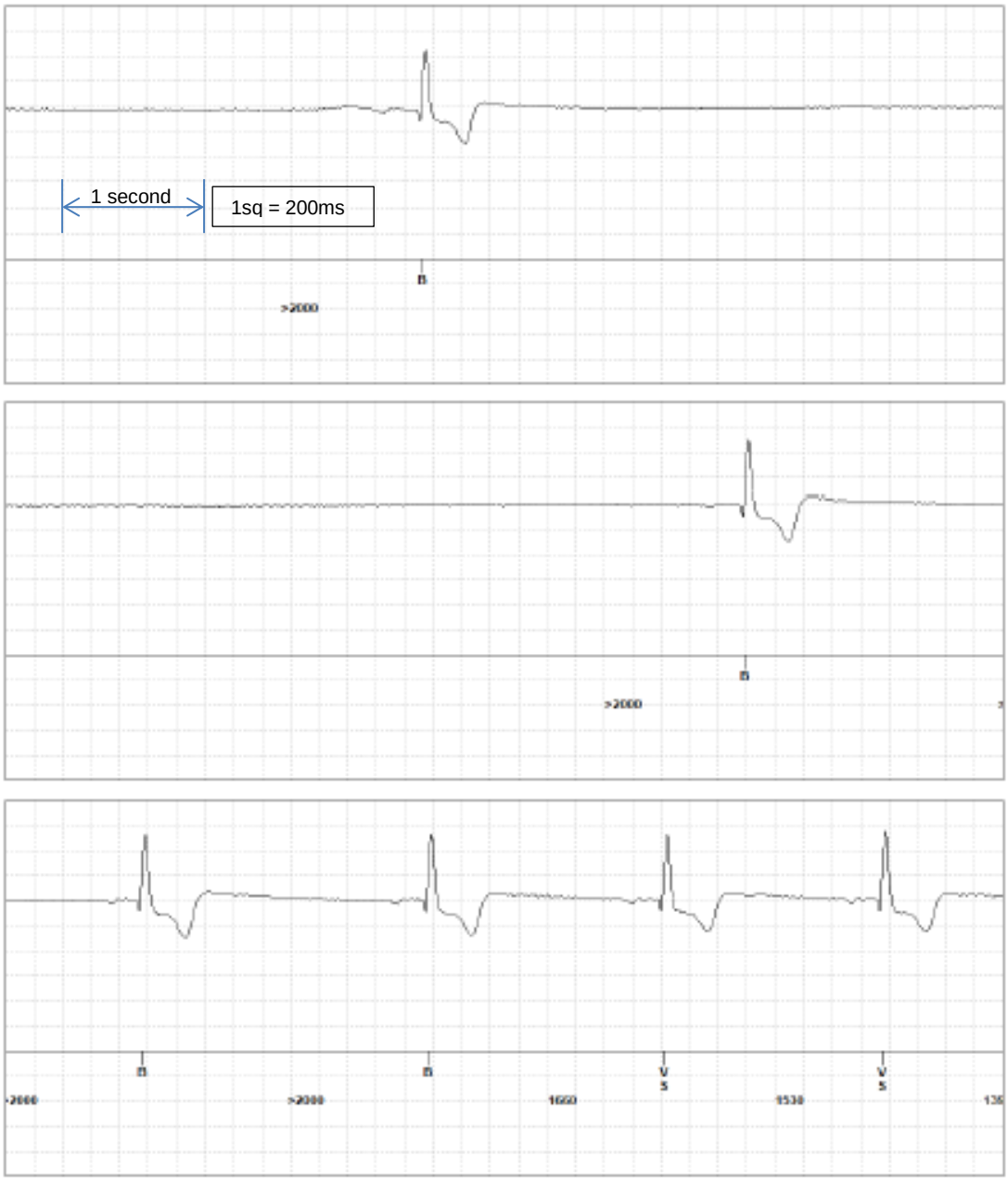


Figure 30 - Asystole



Chapter 7. Conclusions and discussion

In this chapter the RevEAL™ and CARElink™ (Real Care) study will be discussed and explored, and the conclusions presented. In brief the main findings will be discussed, and then the wider results and the inferred possible outcomes will be discussed, followed by implications of the findings, limitations and their impact upon the Real Care study, putting the findings into practice, future research, and personal reflection.

7.1. Main findings of the Real Care study

The primary aims of the Real Care study were to see if the use of remote monitoring with implantable loop recorders (ILRs) could significantly reduce the time taken to follow-up a true event and to achieve a diagnosis with a robust study design.

The study found that the use of remote monitoring led to a statistically significant reduction in time from a true event occurring to the subsequent follow-up, the divergence is evident at all time points in the survival curve of the Kaplan Meier plot (Figure 19) and 50% of patients without home monitoring had to wait at least an additional two weeks before follow-up ($p = 0.004$) (Table 8 and Table 9). Perhaps more importantly the median time from implant to diagnosis was reduced by seven weeks ($p = 0.049$) (Table 10 and Table 11). The only three studies available and reviewed in sections 2.8 – 2.10 (44,45,68) all stated similar findings but only the study by Drak-Hernandez et al. (68) carried out statistical testing to verify this. Their results stated a statistically significant average reduction in time to diagnosis of 204 days ($p < 0.001$). As stated in section 2.10, the study by Drak-Hernandez and colleagues was the most robust study to have been carried out on remote

monitoring of ILRs as it was the only study to have a control group. However the study was neither randomised nor prospective which negatively impacted the robustness of the study. The Real Care study was the first and only registered randomised controlled trial (RCT) with clinician blinding in the field of remote monitoring of implantable loop recorders to date and despite being underpowered the results were still statistically significant.

The evidence (44,45,68) and indeed the Real Care study results in section 6.4 look at first glance to suggest that remote monitoring is superior to conventional follow-up of either three-monthly intervals as in the Drak-Hernandez et al. (68) paper or the six-monthly intervals at County Durham and Darlington NHS Foundation Trust (CDDFT) hospitals. However it could and possibly should be argued that the median time reduction of two weeks for time to follow-up after a true event and seven week median reduction in time to diagnosis are not clinically significant. Additionally it is also important to take into account the cost of the home monitoring equipment, currently £900 per monitor and the additional time required to follow-up patients. There was no formal time in motion analysis carried out as part of the Real Care study but a basic calculation of the time allowed for follow-up suggested a three-fold increase in follow-up time. The current CDDFT method of in-office follow-up (routine or ad hoc) is allocated 30 minutes per appointment. In the experimental group, patients were asked to send transmissions fortnightly or following a symptom. Remote follow-up appointments were allocated 20 minutes; this included contacting the patient by telephone unless prior arrangements were made with the patient to send them a letter if there were no abnormalities. There were 362 follow-ups carried out, 65 for the control

group and 297 for the experimental group. Calculated into hours of follow-up time, that was 32.5 hours for control and 99 hours for experimental group patients. One way that the additional time could be reduced, a method that is in fact being trialled on patients not involved in the Real Care study but who currently use the remote monitoring system, is to only contact them for an additional follow-up if there are any arrhythmias or manual recordings to discuss.

Based on the median time reductions from event to follow-up and diagnosis alone, the above might be interpreted that the benefit of home monitoring in conjunction with ILRs is not as impressive as originally perceived. That might not be strictly true. Closer review of Figure 19 - Survival plot for time from true event to follow-up shows that even those in the experimental group that did not comply with the fortnightly data transmissions, never went more than five weeks before a true event was followed-up. Compare that with patients in the control group and it shows that approximately 35% of the patients in that group waited between five and 24 weeks to have a true event followed-up. The reason for home monitoring patients not going past five weeks before follow-up of a true event is two-fold; firstly the study design required patients to transmit data on a fortnightly basis. Secondly the patients that waited five weeks were a combination of patients that had true event prior to the first follow-up (and randomisation into the study) and non-compliant patients. It is possible that if all patients had been enrolled at implant the five week maximum wait to follow-up would have been less. Even if routine remote follow-up was carried out monthly then the time to follow-up would still be minimal.

A similar picture was revealed on closer inspection of Figure 20 - Survival plot for time to diagnosis by study group. The difference between median time to diagnosis was seven weeks but the divergence of the two groups increased at approximately ten weeks by which point 80% of the experimental group patients that received a diagnosis had received their diagnosis whereas only 52% of the patients in the control group that received a diagnosis had done so. At maximum it took 32 weeks longer for a diagnosis to be reached in the control group. Taking all of the evidence into account and examining the data the suggestion is that remote monitoring of ILRs is not only statistically beneficial but that there are potentially clinically significant diagnostic time reductions also.

Throughout this thesis, particularly throughout the results chapter (Chapter 6) and this section of the discussion (section 7.1) the terms ‘true event’ and ‘diagnosis’ have been widely used but not always in conjunction. This is particularly confusing as not only is the median time from event to follow-up much shorter but also as there was a higher number of patients with a true event (n = 28, Table 17) than there was with patients with a diagnosis (n = 23, Table 18). The explanation for number of true events not being the same as number of diagnoses is slightly more complex, but only slightly; in terms of time from event to follow-up and time to diagnosis, the starting points are different. For time from event to follow-up the starting point of the measure is the date of the event and for time to diagnosis the starting point is the date of implant of the ILR. The explanation for number of true events not being the same as number of diagnoses, the explanation is slightly more complex but only slightly. Not all true events are considered to be clinically significant at

that time and therefore a diagnosis might not be made from such an event. An example of this would be a three second asystole, if the event was nocturnal, or occurred diurnally but in the absence of symptoms then whilst it might be suggestive of a cardiac problem it is not enough evidence to base a diagnosis on.

7.2. Wider discussion of the Real Care results and inferred possible outcomes as a consequence of the study

ILR device memory saturation is a potentially problematic but common finding during follow-up. Saturation of the device memory occurs when artefacts, or undersensing / oversensing of ECG signals causes inappropriate recordings to overwrite previous recordings in the device memory, potentially wiping true event ECGs. One of the key findings in the paper by Furukawa et al (44) was the reduction in device memory saturation made by false ECG detection that could potentially lead to a delay in diagnosis. In their study they found 14% of transmissions to be saturated and they postulated that had their patients been on their standard follow-up pathway (three-monthly in-office checks) that the figure would have been around 45%. Analysis of the Real Care data showed no significant difference in device memory saturation with only a seven percent reduction in memory saturation from 25% down to 18% in the remote monitoring group ($p = .778$). From the analysis of the Real Care results and the data presented by Furukawa et al. (44), it is unlikely that remote monitoring of ILRs would create a truly significant reduction in device memory saturation without severely increasing clinical workload and service cost by increasing the remote transmissions to daily.

Before moving onto the Cox regression analysis of age and gender as determinants of diagnosis, it would be prudent to briefly recap the Real Care study participant demographics as the even distribution of age and gender is preferable for this Cox regression. In brief the participant demographics show that 37 ILR patients had been recruited into the Real Care study. Overall there were 19 male and 18 female with a mean age of 63 ± 16 years and a median age of 63 (36 – 89) years (Table 5). When this is subdivided into the Carelink™ (experimental) group and the control group there were ten male and eight female participants in the Carelink™ group with a mean age of 60 ± 15 years and a median age of 60 (36 – 86) years. In the control group there were 11 male and eight female participants with a mean age of 66 ± 16 years and a median age of 69 (36 – 89) years (Table 6).

Cox regression analysis was used to analyse the Real Care study data with the aim of discovering whether age and / or gender could be used as predictors or determinants of diagnosis in the ILR population. Neither age nor gender could be could be isolated as determinants to suggest a diagnosis would be achieved, but that does not give the complete story. When age and gender were added, the regression suggested that the likelihood of patients with remote monitoring receiving a diagnosis were nearly three times higher (HR = 2.709, p = 0.049, Table 13) than that of patients in the control group despite the study groups being well matched and there being no significant difference between the group demographics. However, if age group was added as a categorical covariate, therefore comparing all age groups (30 – 50, 51 – 70, and over 71) against the baseline group (30 – 50 year olds) then the likelihood of patients with remote monitoring receiving a diagnosis

increased to just over three times (HR = 3.128, p = 0.028, Table 14). This suggests that patients in the baseline age group of 30 – 50 year olds are slightly more likely to receive a diagnosis. The problem with this data is that the study was not powered to address this question and the results could be different if larger group sizes and chance findings cannot be ruled out.

When analysing the diagnostic yield of ILRs, the overall diagnostic yield for the Real Care data analysis was 62% (Table 18). A diagnostic yield of 62% is a figure that is well in excess of the data put forward by Furukawa et al. (73) which included the data of nine studies. Their calculations from the nine studies suggested an average diagnostic yield of 35%. However their data only included cardiac diagnosis and not those in which a non-cardiac diagnosis is made. When reviewing the Real Care data the cardiac diagnosis only yield is 41% (Table 19), still in excess of the average figure.

The results of the Real Care study showed that 19% of the study patients received a pacemaker as a result of findings on their ILR. This means that nearly half of the patients that received a cardiac diagnosis required a pacemaker, a fact that emphasises the move towards early use of ILRs which is recommended in the National Institute of Health and Clinical Excellence (NICE) guidelines (4) and the European Society of Cardiology guidelines (3). In both guidelines the diagnosis of falls and syncope is reliant upon good history taking and the physician being certain that the cause of the syncope is not cardiac. The use of the word ‘certain’ potentially provides a loophole which will increase the use of other tests such as head-up tilt (HUT) or repeated Holter monitoring, however it is also possible that the use of ‘certain’

was used intentionally to guide physicians towards thinking about referring patients to have an ILR therefore allowing a higher chance of diagnostic certainty.

The Real Care analysis highlighted the shortfall in ILR implantation at CDDFT hospitals. The incidence data described in section 1.4 Incidence data on syncope in the UK suggests that CDDFT's implant rate of 150 – 200 ILRs per year is a significant shortfall. Whilst the majority of the patients that receive a diagnosis do not have a life-threatening problem the 41% of ILR patients that have a cardiac diagnosis potentially do have a life-threatening condition, this is particularly true of the 19% of ILR patients that required a pacemaker in this study. One way that has been shown to increase ILR implant rates, and to a lesser extent reduce misdiagnosis, is the introduction of specialist falls and syncope clinics or falls and syncope services and the introduction of visual aids to Accident and Emergency departments that recommend referral of patients with falls and syncope directly to the specialist service (1). This pathway of referral directly to a specialist falls and syncope service could be extended to primary care, giving the healthcare staff in the community setting easy access to falls and syncope services. Not only could this reduce the risk of potentially life threatening arrhythmias in cardiac syncope patients but also reduce the number of unnecessary tests, therefore reducing diagnostic time. In doing this the demand on physiology services would increase with additional tests and device follow–ups. The use of remote monitoring with ILRs could have a role to play in the development of such services as it has the potential to provide a means of screening a large number of ILR patients in a relatively small period of time.

One of the insights gained from the Real Care study was that the number of visits to the Cardiac and Respiratory Department for ILR follow-up appointments could be reduced with the use of remote monitoring. Due to the lack of evidence around this relatively new technology, patients that used the equipment in the study were still required to attend the department for follow-up appointments at six-monthly intervals. Having tested the equipment and transmission reliability there were no major issues found during the study. Therefore it is entirely possible that patients using the Carelink™ remote monitoring system could have some routine appointments removed. Furthermore patients that do not have remote monitoring, that contact the department having either made three manual recordings, or suffered implant symptoms are asked to attend the department for a follow-up. In most cases the appointment given to these patients is an overbooking, which means that patients may be required to sit and wait until they can be seen or that they may not be able to be seen for several days. With remote monitoring these checks can be done without the patient attending the department. However, currently there is no payment tariff for remote monitoring of ILRs and the study / department have taken on the cost of the additional checks. Before a full remote monitoring clinic could be implemented there would need to be arrangements for funding and also time written into the Cardiac Rhythm Management (CRM) rota specifically for the purposes of remote monitoring clinics. In part the cost and time of additional checks could be offset by the inclusion of extra patients. If remote monitoring clinics were set up (in place of in-office clinics) using the 20 minute appointment slots used in the Real Care study then in the average seven and a half hour working day (excluding lunch)

a total of 22 follow-up appointments could be arranged. In comparison to this only 15 follow-up appointments at the standard 30 minutes can be arranged.

Recruitment to the Real Care study was considerably slower than anticipated, the issues surrounding recruitment were not entirely understood initially and the presumption was that this was due to protocol issues as mentioned in section 3.9 and the reduction from two implanting centres and a satellite recruiting site to one implanting centre and a satellite site. While the protocol amendment (section 3.17) did increase recruitment, the study remained under recruited. The decision to remove the second implanting site was made due to workload, staffing changes and differences in practice not allowing for uniformity in recruitment. However, the implant rates achieved at the single implanting centre were well in excess of the number required to power the Real Care study and therefore the impact of this decision was felt to be minimal. Before looking into the issues that were found by reviewing the files of those not included the recruitment figures will be recapped. In total 185 patients received a PIS, 148 (80%) of those were not included in the study. Of that 148 patients, 28 (19%) patients did not meet the inclusion criteria (this included ten patients that received a different ILR device) and 31 (21%) declined to participate. That left 89 patients which was 48% of the overall number of patients that received a PIS, not included in the study. The question then was, why? Various reasons were speculated, the main one being increased clinical pressures and restraints on time. Whilst increasing clinical pressures and time restraints could account for a small percentage of the figure it was unacceptable this was the only reason. A review of the patient files heralded some interesting findings. The main reason for patients

not being included was down to a clinical decision made by the Physiologist or the implanting Physician that it would not be fair to the patient to ask them to use the additional equipment. That decision could be seen as a potential source of selection bias, however patient care is at the heart of everything we do and as practitioners we sometimes feel that it is unethical to ask patients to carry out extra work with extra equipment when they are already struggling to comprehend the equipment that is required for their care. It was clearly documented in 59 (66%) of the patients that they struggled to understand the use of the patient activator and were therefore not suitable for the Real Care study. Additionally 18 (20%) of the 89 patients reported that they had not yet read the PIS at the time of implant (or initial five week check in the case of pre-protocol amendment patients) a subsequent follow-up call was made (in some cases at the next check) to ask the patients if they would like to take part and they reported that they still had not read the information. The remaining 12 (14%) patients had nothing documented regarding the Real Care study and had all been under conventional care for in excess of three months. Due to the lack of documentation and the length of follow-up that had already occurred, no attempt was made to recruit these patients.

The issues surrounding recruitment did however raise an interesting point. Technology is not everyone's strongpoint and had recruitment gone smoothly it may not have been realised that remote monitoring might not suit every individual. When the recruitment data was reviewed, it was suggestive that the current model is not suitable for all patients. One possible solution to this would be for the newest device to be added to the Medtronic™ Reveal™ family, the Reveal™ LINQ™. The new ILR has wireless connectivity and as

such removes the need for patient interaction. Unfortunately, the cost of the device to CDDFT hospitals is between £1700 and £2200 depending on the amount purchased while the Reveal™ XT that is currently used is £1000. The current tender makes the Carelink™ home monitoring equipment a free of charge device to CDDFT and the cost is considerably different. Another possibility would be to offer home monitoring to patients at a 10 to 12 week follow-up as it is after this point that the survival curves for median time from true event to follow-up (Figure 19) and median time to diagnosis (Figure 20) start to diverge considerably and patients have had time to adjust not only to having the ILR implanted but also time to get used to the use of the activator.

7.3. Implications of the findings

The analysis carried out on not only the Real Care data but also the study as a whole suggest that remote monitoring of ILRs is going to become a valuable tool in the future but that current technology, and the infrastructure within CDDFT hospitals Cardiology Services do not allow for a full adoption approach towards remote monitoring. With that said, the currently available technology alongside minimal changes such as reducing the number of in-office follow-ups, a better selection and education process for remote monitoring, and a more refined process for dealing with remote follow-up in terms of when to contact patients has the potential within CDDFT hospitals to:

1. Be good for patients by reducing hospital visits and improving clinic availability therefore giving faster access to all patients.

2. Reduce diagnostic time for ILR patients meaning that they can receive treatment or be referred to the correct specialism faster.

3. Reduce clinic workload but increase the number of patients reviewed.

There are unfortunately potential negative implications too suggesting that:

1. Remote monitoring is not currently suitable for all ILR patients due to the requirement of patient interaction with the equipment.

2. Patients need to be selected carefully; some of the patients requiring an ILR are older, frail, or unable to fully understand the importance or the use of the equipment.

The reason the above points are referred to as potentially negative is that they can also be turned quite easily into positives. Technology is moving forward and as the newer devices such as the Medtronic Reveal™ LINQ™ become more widely available remote monitoring will become more suitable for all ILR patients. As for the second point, ignoring the possibility of everyone getting the newer technology in the future, there are changes that can be made now to explore the use of home monitoring fully in the patient group that have thus far been excluded. Many of the patients that are very frail, or cannot understand the equipment have carers or relatives that visit frequently, or attend follow-up appointments with the patient. This can be logistically challenging and sometimes stressful. Perhaps it would therefore be more

appropriate for the relative / carer of these patients to be taught how to use the equipment and for these patients to be monitored remotely.

7.4. Limitations of the Real Care study

As with all studies the Real Care study was not without its limitations. The lack of recruitment led to the first limitation in that only 50% of the patients required for the study to be at full power (90%) were recruited. Due to the fact that the study still found significant reductions in time from event to follow-up and time to diagnosis the effect of this limitation is believed to be minimal. Recruitment and recruitment issues are discussed in detail in sections 7.2 and 7.5 in this chapter.

A further limitation to this analysis (not the study overall) is that some patients had not reached full follow-up time due to the staggered entry of patients inherent in this type of study.

7.5. Impact of limitations upon the results

The impact of these limitations upon the Real Care study's results is open to interpretation; while the results could well be underpowered the information gained was still statistically significant and could be seen as a valuable step forward in the field of remote monitoring of ILRs. There is also the argument that the exclusion of so many patients could be a source of selection bias. The effect however would be minimal on the comparison data due to the randomisation process and the groups remaining significantly similar.

The lack of a complete follow-up period for some patients in the study could possibly have an impact upon the results but the analysis of this data and previous studies is suggestive that the trend would continue and that the results would either be similar or improve the superiority of remote monitoring.

It is worth mentioning again at this point that despite being underpowered the Real Care study still demonstrated a statistically significant reduction in both time from true event to follow-up and time to diagnosis using a robust design which until this study had not been done.

7.6. Putting the findings into practice

In their paper on the use of remote monitoring with ILRs Arrocha et al (2010) stated that remote monitoring could be burdensome to staff (45). While no formal time in motion study was carried out as part of this thesis, both the author and other members of the Cardiac Rhythm Management (CRM) team agree that in its current format whereby patients are contacted following their data transmission and essentially have a complete follow-up over the telephone, or a letter is dictated or typed requires an allowance of time that with current staffing levels would be difficult to sustain, particularly if the numbers of end users was to increase. It was previously mentioned in this chapter a possible solution or minimisation tool for this problem is being trialled, patients that are using remote monitoring but were not part of the Real Care study are only being contacted after a transmission if there are any symptom recordings or any arrhythmias to discuss, and if merged with an improved selection and initiation process, remote monitoring would still be an impressive tool for reducing diagnostic time and improving patient care.

In order to maximise the effect of remote monitoring, several changes would be required in CDDFT hospitals. These changes would need to be managed effectively for the full potential of remote monitoring to be reached. Some of the initial changes to services that would allow for a robust remote monitoring service have already been mentioned in this chapter; firstly the selection criteria and the timing of introduction of the equipment would need to be decided. One possible suggestion from reviewing the available data and the results of the Real Care study is that the idea of remote monitoring could be introduced on the day of implant and then patients could have the equipment explained and given at the five-week follow-up. This would serve several purposes. Firstly this approach would allow patients to consider their options and could reduce an element of fear that can surround technology. Secondly it would be the ideal opportunity to suggest that the patient brings a relative or carer to the appointment. This in turn would allow patients that are currently deemed unable to use the equipment to be included. This approach would also allow for the five-week follow-up to have an increased appointment time where patients have an opportunity to get a full demonstration of the equipment and have any questions or issues discussed. Patients would be asked to send their remote monitoring recordings as per the Real Care study (fortnightly or following symptoms) and would be advised that contact would only be made if a manual recording was present or if the recording needed to be discussed. The next step would be to create clinics or an allocation of time within clinics dedicated to remote follow-up. This could incorporate all remotely monitored devices and system administration (currently an adhoc process) not just ILRs therefore ensuring that time is utilised effectively. However, in order to make these changes and potentially switch to a remote

monitoring service with minimal physical patient attendances to the clinic, discussions need to be had around the introduction of a tariff that will cover the cost of the service and some work will need to be carried out with the staff on change management.

If services such as specialist falls and syncope services or improved care pathways were introduced that potentially increased implant rates, then services would require alterations just to meet demand. The possibility of increasing the availability of available services has already been discussed in this section and could easily be incorporated into plans to expand and improve patient care for falls and syncope.

Whilst not a finding of the Real Care study, the research process and in particular the literature review that I undertook as part of this thesis, has directly led to changes in the programming methodology of ILRs at Darlington Memorial Hospital where I am currently a cardiac physiologist. Previously it was common practice to set the bradycardia detection limit to only record rates ≤ 30bpm. After reviewing the literature, it was put forward by the author of this thesis that this was too stringent and allowed the team to potentially miss significant bradycardias. This point was accepted by the clinical team and the bradycardia detection rate is now set to record rhythms at a rate of ≤ 40bpm in line with the ISSUE classification (69) as standard.

7.7. Future research

Whilst the evidence supports the use of remote monitoring of ILRs there are still areas that require further work. This study became underpowered due to recruitment; the suggestions made in section 7.6 Putting the findings into

practice introduced a possible way for more ILR patients to be included. This would allow for a larger trial to be conducted. Currently the results of this study, while believed to be transferable are only tested on the CDDFT ILR population; a larger multicentre trial would be able to prove whether or not the results were fully transferable.

There is also scope for some qualitative research related to ILRs and remote monitoring, do patients feel that they are getting the best care if they are no longer required to be seen every six-months? Is there any impact upon quality of life (QoL) between those patients that have a conventional follow-up pathway and those that have remote monitoring? The evidence (44,45,68) including this study suggests that remote monitoring has a role in patient care but do the patients believe it adds any benefit to their care? The QoL and additionally psychological research could also be broadened into just the impact of ILRs. A search of PubMed, Medline, Ovid, Allied and Complementary Medicine (AMED), Excerpta Medica Database (EMBASE), Health Management Information Consortium (HMIC), British Nursing Index (BNI), PsycInfo, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Health Business Elite and Google returned no hits relating purely to ILR patients and QoL or psychological impact of having an ILR and waiting to be symptomatic. When you consider that patients on conventional care are implanted with a device, and then essentially told to go away and have another symptom (predominantly syncope), there is potential for this to impact upon their life. Anecdotally when speaking to ILR patients in follow-up clinics many of the patients report that they do not like to go anywhere alone, or in

severe cases do not want to leave the house at all for fear of having a syncopal episode.

Another area of future qualitative research could look at the clinical staff perspectives of remote monitoring, do they think it is diminishing care by taking the patient contact away from the job, or do they think it improves the patient care pathway? Do clinical staff think remote monitoring is an important step towards the future or just a gimmick that will become too time consuming to be of use?

7.8. Personal reflection

When reflecting on the journey undertaken to reach this point, it is easy to dismiss elements that while key at the time, seem to pale in comparison to the greater issue of recruitment. However most of the elements were entwined with recruitment at the time and it is only now, on reflection, that realisation can fully occur. Recruitment was initially seen as a constant embarrassment and always a point that rose at trial meetings and supervisory meetings. It was only at the point of analysis that the importance of the under recruitment was highlighted. Time was spent attempting to right a wrong that was in reality an important factor relating to the technology used in the Real Care study. It showed that the team actively involved in the study were enthusiastic about the technology and the change it could bring with it, but emphasised the fact that not everyone is the same. People are individuals and not all individuals embrace change in the same way. A simple and well known premise but one that is easily overlooked, as told to me many years ago during training, a phrase that sticks with me is “Always remember to go back

to the basics". At the time and for many years I associated it with diagnostics and if I was troubleshooting a problem would look at the basics first and not jump straight in to the more technical possibilities. It is only now that the full meaning of those words is becoming clear. As a researcher it is easy to embrace technology and even to embrace change with the thought at the back of the mind that just because something has always been done a particular way it is not necessarily the best way. The basics of human emotion and thought however mean that not everyone is curious about change and that an innate fear of change or a desire for sticking to what is known, or comfortable is preferential. The approach towards the Real Care study was created and reviewed by researchers of like minds. Whilst there was diversity within the team, reflection would suggest the inclusion of those that are openly sceptical of change or research in order to create a better balance although this would probably have slowed things down. Perhaps if the trial was to be carried out again it would be beneficial for sessions to be held with the doctors, physiologists and nurses on change management and to have sessions with the patients to introduce them to the technology in a relaxed environment rather than in a clinic setting or directly after they have been through a procedure.

Chapter 8. Concluding remarks

In this final chapter the concluding remarks of the thesis are presented as a summary of the main conclusions, limitations and next steps.

8.1. Main Conclusions

The first conclusion to be drawn from the analysis of the REveAL™ and CARElink™ (Real Care) study is that remote monitoring can be effective in reducing both diagnostic time and the time taken to detect a true event ECG for implantable loop recorder (ILR) patients. However further discussion is required as to whether the reduction is clinically significant in the majority of cases.

The second conclusion which in all likelihood is actually more important than the first as it has potential to dramatically influence the first; technology is not every patients' strongpoint, and that in the larger population of ILR patients the currently available mainstream method of remote monitoring for ILR patients is not an attractive option. Once the technology of the Reveal™ LINQ™ with its wireless capability is available to all patients, the full potential of remote monitoring could be realised.

Finally, until the new technology becomes available to all, a new process of patient selection and management could maximise the impact of remote monitoring on diagnostic time reduction whilst increasing patient uptake of the service.

8.2. Limitations

One of the biggest limitations became one of the most important findings in the Real Care study. Recruitment initially thought to be predominantly a process issue in fact uncovered a possible failing of the technology believed to be suitable for the majority of patients. Not all patients adapt well to new technology and there has to be a line at which we do not ask more of the patients. During the review of patients not included in the Real Care study it became clear that a high percentage of our patients struggled with the use of technology that was designed to aid their care. In this case it was when explaining the use of the ILR activator to the patient following the implant of their ILR that highlighted the problem. Sometimes the things we believe to be simple are in reality only simple to those that understand the process already.

8.3. Next steps

Moving forward there is a potential need for a larger multicentre trial with a qualitative aspect to review patient benefit in terms of quality of life (QoL) and perceived benefit of care. In terms of reducing diagnostic time and relieving pressure on clinics at County Durham and Darlington NHS Foundation Trust (CDDFT) hospitals there is a good level of evidence to suggest that with correctly managed minimal changes to the current care pathway, a reliable and safe alternative to the current regime could be introduced successfully. In fact changes have already begun to take effect due to the findings of this study.

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Appendices

Appendix 1 - Real Care Protocol

Reveal™ and Carelink™ (Real Care)

Does Using Remote Monitoring in Combination With Implantable Loop Recorders Reduce the Time to Diagnosis? A Randomised Controlled Trial

Gareth Pounds Cardiac Physiologist BSc(Hons).

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Abbreviations

AF	Atrial Fibrillation
AT	Atrial Tachycardia
AV	Atrio-Ventricular
CDDFT	County Durham and Darlington NHS Foundation Trust
CRT	Cardiac Resynchronisation Therapy
ECG	Electrocardiograph
ESC	European Society of Cardiology
FVT	Fast Ventricular Tachycardia
ICD	Implantable Cardioverter Defibrillator
ILR	Implantable Loop Recorder
ISSUE	International Study on Syncope of Uncertain Etiology
NICE	National Institute for Health and Clinical Excellence
p	Probability
PICTURE	Place of Reveal™ in the Care Pathway and Treatment of Patients with Unexplained Recurrent Syncope
PII	Patient Identifiable Information
PM	Pacemaker
QoL	Quality of Life
SD	Standard Deviation
SVT	Supraventricular Tachycardia
TLoC	Total Loss of Consciousness
VT	Ventricular Tachycardia

1.0. Introduction / Rationale

Implantable loop recorders (ILRs) are small diagnostic devices for recording electrocardiographs (ECGs) for extended periods (in some cases up to 36 months)(Brignole et al., 2009). The ILR device is implanted using local anaesthetic in the subcutaneous tissue of the left hemithorax (Parry and Matthews, 2010). The indications for the use of ILRs include, but are not limited to, the diagnosis of unexplained syncope or transient loss of consciousness (TLoC) where cardiac involvement such as an arrhythmia is suspected or indicated but not confirmed (Iglesias et al., 2009), palpitations, and observation-guided management of atrial fibrillation (AF) patients (Brignole et al., 2009). In many cases the use of ILRs comes after the repeated use of tests such as Holter monitoring or external loop recorders, however in some cases, the European Society of Cardiology (ESC) and The National Institute for Health and Clinical Excellence (NICE) suggest early use of ILRs. Both NICE and the ESC state that after initial assessment and subsequent cardiovascular assessment by a suitable person or physician, if TLoC/syncope occurs infrequently (less than once every two weeks) and is believed to be due to cardiac arrhythmia or remains unexplained then an ILR should be employed (Moya et al., 2009; NICE, 2010b). Results from the Place of Reveal™ in the Care Pathway and Treatment of Patients with Unexplained Recurrent Syncope (PICTURE) study demonstrated a high diagnostic yield from ILRs and suggested that the devices were under-utilised in clinical settings and that better adherence to guidelines could reduce the wasted tests and consultations that many patients go through (Edvardsson et al., 2011). It has also been suggested that if ILRs are used as laid out in the guidelines produced by NICE (2010b) in the UK, they are cost effective (Davis et al., 2011). While ILRs are considered an effective tool the recorders suffer from memory saturation, meaning that events are logged but not available for analysis, this is in part due to over-sensing and under-sensing (Iglesias et al., 2009). The current method of in-office follow-up promotes saturation and potentially prolongs diagnosis and/or treatment (Furukawa et al., 2011; Arrocha et al., 2010).

The annual incidence of patients presenting with syncope in a UK setting has been estimated at approximately 2.7 per 1000 population (Farwell and Sulke, 2004). With a population of just over 605,000 (Health Protection Agency, 2012) in the County Durham and Darlington area, that would imply that around 1,635 patients within the CDDFT catchment area will have a syncopal episode each year. It is further suggested that 259 (16%) (Farwell and Sulke, 2004) of these patients will have an arrhythmic cause for their syncope. While these are estimated figures on the incidence of syncope it is also reported that due to misdiagnosis of epilepsy and other causes of TLoC the real figures could be 20-30% higher (Brignole et al., 2009; NICE, 2010b). In a costing statement carried out by NICE (2010b) it was reported that estimating the number of patients that require an ILR is not possible for the same reasons, as any figures could potentially be an underestimation.

A recent advance in ILRs has made the use of remote monitoring available as an alternative, or as a supplement to in-office follow up. There is readily available research on the effective use of remote monitoring with other implantable

cardiac devices such as implantable cardioverter defibrillators (ICDs), cardiac resynchronisation devices (CRTs) and pacemakers (PMs) (Santini et al., 2009; Nielsen et al., 2008; Joglar, 2009; Pekka Raatikainen et al., 2008; Marzegalli et al., 2008). Remote ICD monitoring has proved to be valuable for patients and clinical staff in recent years, especially in light of problems with ICD lead systems such as St Jude's Riata family of leads or Medtronic's Sprint Fidelis lead. Remote monitoring has now been recommended as a valid safety tool (Beukema et al., 2010; U.S. Food and Drug Administration, 2011). Due to the infancy of remote monitoring in ILRs there is still very limited data available (Furukawa et al., 2011).

Currently County Durham and Darlington Foundation Trust (CDDFT) hospitals follow up ILRs at 1 month post implant and then at 6 monthly intervals as per departmental policy. Anecdotally it is suggested that other centres in the region have less frequent protocols for ILR follow-up with some centres only following up annually and others only following up if symptoms occur. Furukawa et al (2011) suggest that the optimal way to follow up ILRs is by remote monitoring at weekly intervals as this reduces the amount of memory saturation, meaning that possibly relevant ECG information is not overwritten by false events. Others believe that while remote monitoring may have a role in ILR follow up the frequency of transmissions may create an excessive burden on clinical staff (Arrocha et al., 2010).

A recent service evaluation of remote monitoring of ILRs using Carelink™ within the CDDFT hospitals, has suggested that it is well accepted among our patient population with a compliance rate of 94%. When the data obtained from this service evaluation was compared to data from an audit of ILR patients within the CDDFT hospitals it suggests that time to detection of a true event and therefore patient diagnosis, using the traditional CDDFT follow-up protocol may be prolonged. The median time to detection of a true ECG using the traditional follow-up data was 30 (0-204) days while the Carelink™ patients showed a median time of 6 (0-8) days. Patients taking part in the service evaluation were asked to send a transmission on Carelink™ monthly. This however still led to device saturation and a slight delay in diagnosis of a true event; for this reason it has been suggested that fortnightly downloads of data will be most appropriate.

1.1. Lay Summary

There are many reasons why people collapse or suffer from palpitations. After full investigations there may be suspicion but not evidence that it is due to an irregularity in the rhythm of the heart. If the heart is going too slowly or too fast, it could be the reason for the collapse. A patient's doctor may suggest prolonged monitoring of the heart by means of an implantable loop recorder. The implantable loop recorder is a small device that can record the heart's rhythm and rate for up to 3 years.

The aim of this study is to compare traditional methods of implantable loop recorder follow-up within the County Durham and Darlington NHS Foundation Trust hospitals with a newly available method that means patients can be

followed up from their own home. This study aims to find out which method reaches a diagnosis quicker.

1.2. Conventional Care

In CDDFT hospitals, once a patient has had their ILR implanted, they are seen by a Physiologist. The Physiologist will programme the patient's name, date of birth, and their implanting hospital and Doctor's details into the device via a programmer using telemetry. Once the details are in the Physiologist will explain the use of the manual activator, this is a separate device (about the size of a standard packet of cards). The patient presses the single button on the activator, the activator will then illuminate a picture of a white heart which indicates that the activator is ready. The activator is then placed over the site of the ILR on the patient's chest. The activator beeps and displays a green tick next to the white heart which indicates that the process was successful. Once the patient is happy and has demonstrated that they can use the activator the Physiologist will use the programmer to interrogate the ILR and erase the demonstration recordings. All ILR patients are given an identification (ID) card that has details of the device they have implanted and the implanting hospitals details. Patients are advised that they will need to carry the ID card with them at all times, especially if they are going abroad. On the reverse of the card there are instructions on the use of the manual activator.

Before the patient leaves the hospital after their implant, they will receive an appointment at their chosen CDDFT hospital to see a physiologist one month after their implant. After the one month appointment patients are seen every six months by a physiologist at their local CDDFT hospital at a Cardiac and Respiratory Services Department. All patients are given the telephone number of their local Cardiac and Respiratory Services Department and advised to call if they use their manual activator, patients are normally seen within 24 hours of contacting the department.

At all appointments patients will be asked how they have been since their last visit and if they have had any symptoms. The physiologist will then check the implant site to make sure that the wound has healed properly (first four to six weeks) and that there is no signs of infection, erosion or migration of the device. The Physiologist will then interrogate the device with the programmer and review any ECG recordings. If there are any significant recordings the physiologist will contact a Cardiologist and present the findings to them. If the patient's medical notes are not present then these will be ordered at this time. All data from the device is stored to the patient's disk and the patient's departmental device file is updated. If there are no significant recordings then the patient's disk and file are updated and the patient is given an appointment to come back in six months for routine follow-up.

All follow-up appointments are carried out by qualified Clinical Cardiac Physiologists and escalated to a Cardiologist if necessary.

2.0. Research Question / Aims

The main aim of this study is to answer the research question:

'Does remote monitoring of ILRs reduce the time taken to reach a cardiac / non-cardiac diagnosis in symptomatic patients?'

This will be achieved by comparing the data obtained by two methods:

i. In-office follow-up.
ii. Remote follow-up.

This study will also look at the diagnostic yield of ILRs within the CDDFT hospitals where the research is to be carried out and assess the impact that remote monitoring may pose to the Cardiac Diagnostics Service in terms of time and resource.

3.0. Null Hypothesis

'Utilising Carelink™ remote monitoring for CDDFT ILR patients does not reduce the time taken to reach a diagnosis of whether there is a cardiac cause for their symptoms or not, when compared to traditional in office follow-up.'

4.0. Objectives

4.1. Control Arm Data

All devices will have their follow-up data stored at follow-up as per current protocol of completing the follow-up form (Appendix 1), printing ECGs and storing device data to disc. The Chief Investigator (CI) will then anonymise the data and use it to create a database to show:

Time to the first true event ECG from implant in days.
ii. Time from first true event ECG to next follow up in days.
iii. Burden of false event ECGs.
iv. Device memory saturation.
v. The action taken in response to a true event ECG / Outcome.

Details of anonymisation are covered in section 5.6. Data Anonymisation.

4.2. Carelink™ Arm Data

Patients using the Carelink™ remote monitoring equipment will be asked to carry out fortnightly downloads of their ILRs or symptom downloads if they use their device activator to manually record an ECG at the time of symptoms. The transmissions received via the Carelink™ system will be anonymised and added to the database by the chief investigator, ensuring the parameters measured are the same as the control arm data.

4.3. Events, Symptoms and ECGs

An ECG recorded on an ILR, whether it is recorded automatically or manually is considered as an event. Events are classified as true or false (see section 6.2 for a detailed description), and correlated with symptoms where possible.

Symptoms are broadly considered to be, loss of consciousness, dizzy spells or palpitations. However for reasons of patient safety, other symptoms that could have a cardiac cause, such as shortness of breath or chest pain will not be ignored and patients will be reviewed on an individual basis.

4.4. Diagnosis / Outcome

A participant is considered to have a cardiac diagnosis if they are treated for a cardiac problem that could be the cause of their symptoms, such as asystole, bradycardia or tachycardia other than sinus tachycardia. Treatment could be in the form of medication, a cardiac device (pacemaker, ICD or CRT) or any other form of cardiac rate or rhythm management therapy. Participants may receive a non-cardiac diagnosis as the cause for their symptoms, this is considered to be the case if a participant makes a manual recording whilst symptomatic on two or more occasions. Finally, previous data suggests that there will be a small number of participants that will not have any symptoms during the 24 month follow-up period, these participants will receive no diagnosis.

4.5. Data Analysis

Data analysis will be carried out after the last enrolled patient has undergone 24 months of follow-up. However aggregated summary data will be reviewed and monitored by the R&D auditors and the Trial Steering Group.

5.0. Study Design

This will be a prospective, randomised, clinician blinded, study to be carried out within CDDFT hospitals, using consecutive and fully informed patients. Data analysis is to be carried out on an intention to treat basis, therefore all patients that complete the study will be analysed in their respective group, regardless of crossover or non-compliance.

5.1. Sample Size

The sample size required for this trial was calculated using data collected in a recent audit of CDDFT ILR patients on conventional follow-up, and the joint decision arrived at by the research team, that in order to make a trust wide remote monitoring service viable a reduction in diagnostic time of 50% would be required. Data from a recent service evaluation suggests that a 50% reduction is a realistic possibility but was not powered and was not robust enough to prove this.

Prior data indicates that 85% of patients on conventional (control) ILR follow-up have not received a diagnosis after 12 months. It is hypothesised that this can be reduced to 43% of the patients, using Carelink™ remote (experimental) follow-up over the same time period. Using the software program nQuery7 and a log rank sample calculation for proportional reduction total of 60 patients are required to enter this study, 30 patients into the Control arm and 30 patients into the Carelink arm. The alpha (α) error set to 0.05 and the beta (β) error set to 0.9, giving a two tailed significance of 5% and a power of 90%. Table 1 shows the nQuery7 output.

Table 1 – nQuery7 output

Test significance level, Æ	0.05
1 or 2 sided test?	2
Group 1 proportion, ÒÁ	0.85
Group 2 proportion, ÒÂ	0.43
Odds ratio, Ø = ÒÂ (1 - ÒÁ) / [ÒÁ (1 - ÒÂ)]	0.133
Power (%)	90
n per group	30

As a precaution to allow for dropouts and loss to follow-up, an additional 10 patients per group will be enrolled into the study. This will give a total of 80 patients in the study and 40 patients per group.

The sample size decisions have been reviewed and approved by Dr Douglas Wilson, Statistician at Durham University, School of Medicine, Pharmacy and Health.

5.2. Recruitment

Using previous implant and growth rates it is predicted that 95 ILRs will be implanted in the 2012/13 financial year with a further significant increase in the 2013/14 financial year.
After assessment of current implanting data, a recruitment period of 24 months will be employed in this trial.

All implanted patients will be asked if they wish to enrol. The patients that choose not to enrol will continue with standard in-office follow-up and their care will not be affected in any way.

5.3. Inclusion Criteria

Patients implanted with a Medtronic DX or XT ILR at CDDFT hospitals that:

Are aged 18 years or over
ii. Have access to a landline telephone
iii. Are themselves cognitively capable to consent.
iv. Have the ability to use the manual activator and Carelink™ equipment or a willing and appropriate adult to do so for them

v. Are able to communicate and understand instructions given in English.

5.4. Exclusion Criteria

Patients will be excluded from the study if:

They do not have access to a landline telephone
ii. If they have documented cognitive impairment that means that they are unable to consent.
iv. Are unable to comply with the use of any equipment.
iii. Patients that may be considered for Carelink™ for geographical reasons.
v. They cannot communicate or understand instructions given in English.

5.5. Endpoints

The clinical endpoints of this study are:

Time to diagnosis/outcome.
Device removal for any reason.
Death.

For an endpoint to be considered it must occur within the 24 month follow-up period of the study.

5.6. Data Anonymisation

All relevant data will be transferred from the patient's medical notes and departmental loop recorder file on to an analysis spreadsheet (spreadsheet A). This spread sheet will hold only non-patient identifiable data. During the collection process the patient's study number will be used to link the patient to the spreadsheet. A second spreadsheet (spreadsheet B) containing all patient identifiable data used in the study (name, date of birth and hospital number) will also be created. Once the study is complete spreadsheet B containing the patient identifiable data will be destroyed and patient study numbers will be removed from spreadsheet A containing the analysis data. Patients that requested copies of the findings of the study will have their contact details retained until they have received their copies of the reports.

All spreadsheets will be created and managed by the Chief Investigator and subsequent anonymisation will also be carried out by the CI. The CI will have responsibility for ensuring patient data is handled appropriately and that only anonymised data is presented to those outside of the research team and the direct care group.

5.7. Data and Data Protection

During the trial patient identifiable data will be available to the Chief Investigator and relevant medical staff only. Once data has been anonymised it will be available to the Chief Investigator and the supervisors. All patient

information will be accessed and handled in a confidential manner. Any hard copies of data will be stored in a locked filing cabinet in a locked department at one of the research sites. All electronic information that contains PII will be stored on a password protected networked CDDFT PC, CDDFT encrypted laptop or Medtronic's secure server. Anonymous data will be stored on password protected networked CDDFT PC's, CDDFT encrypted laptops or CDDFT encrypted USB memory sticks.

Patient data will be kept secure at all times in accordance with the data protection act and local/national NHS information governance criteria.

6.0. Method

Patients that are going to receive an ILR will attend a pre implant assessment, this is usually carried out one week before the implant. At this appointment the pre assessment nurse will inform the patient that we are conducting a research trial and asked if they would like to receive the study invitation and patient information sheet (PIS) (Appendix 2 shows an example version). On the day of implantation of their ILR, patients will be asked if they would like to join the study. If a patient would like to join they will be given the opportunity to ask any questions and asked to verbally consent to having the inclusion and exclusion criteria applied, this will only be carried out by a member of their direct care team that already has access to their medical notes. The patient will then be asked to sign the consent form (Appendix 3 shows and example version). On attendance to this appointment the patient will have had a minimum of 48 hours breathing space to consider their position before giving consent or otherwise. A letter will be sent to the patients' GPs (Appendix 4) to inform them of their patient's participation in the trial along with a copy of the PIS.

6.1. Randomisation

Once patient consent and eligibility to join the trial are confirmed they will be allocated a study number and randomised to either the control arm or Carelink™ arm. Randomisation for this trial will be carried out in a block randomisation method using blocks of four on a 1:1 basis in order to maintain similar patient numbers in each group.

A randomisation table will be generated by Dr Douglas Wilson Statistician and held by an independent person within CDDFT. Researchers will contact this person once a patient is enrolled. The patient's study number will be compared to the randomisation table by the independent person and the patient will then be allocated to the control or experimental arm. All correspondence will be logged and researchers will at no point have access to the randomisation table, in order to maintain concealment an SOP will be developed and adhered to.

6.2. Control Arm Methods

The patients in this arm will be asked to follow the conventional CDDFT care pathway. They will be seen every six months in one of the three CDDFT Cardiac and Respiratory Services Departments and additionally if they have a symptomatic event. The investigator will review all ECG strips, both manually and automatically stored. The ECGs will be classified as true or false (see Table 2) using an adaptation of the classification table put forward by the International Study on Syncope of Uncertain Etiology (ISSUE) investigators (Brignole et al., 2005) seen in Figure 1. The number of recordings without ECGs will also be recorded in order to calculate device memory saturation. The investigator will then record the time in days from ILR implantation to the first true ECG, the time in days from the first true ECG to the nearest follow-up. The number of follow-ups and total follow-up time will also be recorded as will the outcome or response to a true event. The data will then be used to construct a database for use in the statistical analysis. All true events will be assessed by the Chief Investigator and/or a Senior Cardiac Physiologist then reviewed by a Cardiologist. The Cardiologist will be blinded to which arm of the trial the patient is in. All follow-up data will be documented on the Real Care follow-up sheets (Appendix 5).

Outcomes will be classed as positive, negative or none. A positive outcome is for patients that receive a cardiac diagnosis, a negative outcome is for patients that can be confirmed not to have a cardiac cause for their symptoms and none is for the few patients that do not have a symptom or true event during the follow-up period.

Table 2 – The departmental ECG classification criteria for the current study adapted from the ISSUE classification table (Brignole et al., 2005).

True Events	False Events
FVT or VT recording showing a tachycardia ≥120bpm, conclusively or believed to be a rhythm other than sinus tachycardia.	FVT or VT recording showing sinus tachycardia or artefact.
Asystole recording showing an R-R pause of ≥3 seconds (for AF ≥3 seconds diurnally and ≥4.5 seconds nocturnally)	Asystole recording with evident under-sensing.
Bradycardia recording with a sudden decrease in heart rate of >30% or <40bpm for ≥10 seconds.	Bradycardia recording with evident under-sensing.
Manual recordings displaying any of the above, or Manual recordings showing no significant ECG changes / false events but recorded in the presence of patient symptoms.	Manual recordings displaying any of the above, or no significant ECG changes if recording is made in the absence of symptoms or in the presence of symptoms not related to ILR implantation.

Figure 1 – The ISSUE classification table.

Table 1 The ISSUE classification of ECG-documented spontaneous syncope

- ***Type 1 Asystole.*** RR pause ≥ 3 seconds
  - → *Type 1A, Sinus arrest:*
    - – Progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest
  - → *Type 1B, Sinus bradycardia plus AV block*
    - – Progressive sinus bradycardia followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate
    - – Sudden onset AV block (and ventricular pause/s) with concomitant decrease in sinus rate
  - → *Type 1C, AV block*
    - – Sudden onset AV block (and ventricular pause/s) with concomitant increase in sinus rate
- ***Type 2, Bradycardia.*** Decrease in heart rate >30% or <40 bpm for >10 seconds
  - → *Type 2 A.* Decrease of heart rate >30%
  - → *Type 2 B.* Heart rate to <40 bpm for >10 seconds
- ***Type 3, No or slight rhythm variations.*** Variations of heart rate <30% and heart rate >40 bpm
  - → *Type 3 A.* No variation or <10% variation in heart rate
  - → *Type 3 B.* Increase in heart rate >10% but <30% and <120 bpm; or, decrease >10% but <30% and >40 bpm
- ***Type 4, Tachycardia.*** Increase in heart rate >30% or >120 bpm
  - → *Type 4 A.* Progressive sinus tachycardia
  - → *Type 4 B.* Atrial fibrillation
  - → *Type 4 C.* Supraventricular tachycardia (except sinus)
  - → *Type 4 D.* Ventricular tachycardia

(Brignole et al., 2005)

6.3. Carelink™ Arm Methods

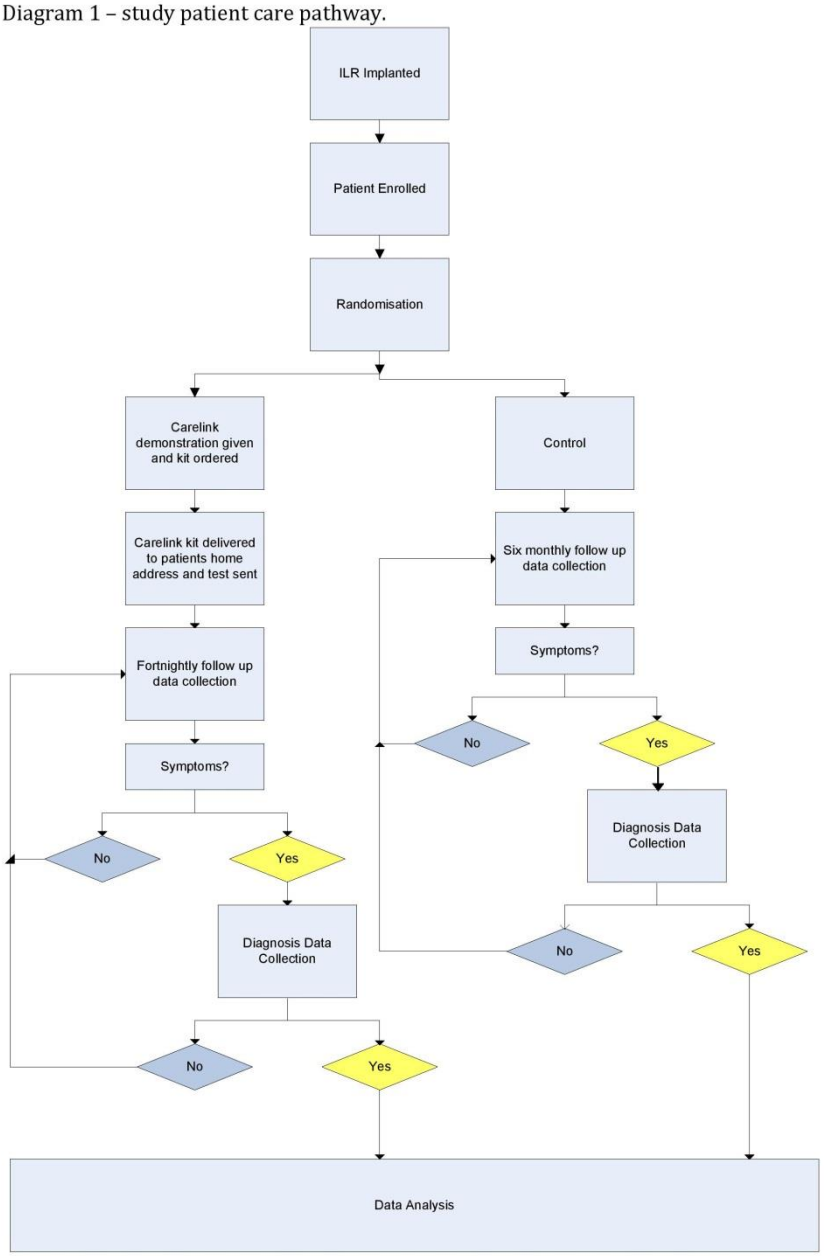
The patients in this arm will be given a demonstration of the equipment. The explanation will detail how to connect the equipment to the phone line, where to place the telemetry header of the equipment and how to activate the equipment to send their data to the secure server. When the patient is happy and all questions have been answered they will be asked to sign a further consent form issued by Medtronic (further details of the server, data handling and Medtronic consent form are available in section 7.2 and appendix 6). Patients will be asked to send transmissions fortnightly throughout the study. The data obtained will be assessed in the same way as the control arm data. Patients will then be contacted by telephone or by letter (only if non-urgent/routine) if they are not available on the phone. Patients will be contacted the same day where possible. All data will be stored in the patient's departmental device file, and patient's medical notes will be requested when findings are significant, as per the department's Standard Operating Procedure (SOP)

In addition all administrative and clinical time required to run the Carelink™ method of follow-up will be logged in order to assess the impact of Carelink™ as a service addition.

6.5. Study Care Pathway

Diagram 1 shows the care pathway for study patients highlighting when data collection will take place.

Diagram 1 – study patient care pathway.



6.6. Statistical Methods

All of the statistical calculations and analysis will be carried out using the Statistical Package for the Social Sciences (SPSS/PASW) 20 or 21 computer package.

The data acquired will be used to measure the proportional shift between the Control arm and Carelink™ arm observed events and time to diagnosis. The data will then be used to generate survival curves for the two groups. Survival analysis will be carried out and survival times and hazard ratios calculated. Results will be considered significant if the two-tailed probability is ≤ 0.05. Logistical regression analysis will also be carried out with data stratification to see if risk factors can be considered. However due to limitations in patient variables such as not attending clinics and inability to use equipment the statistical methods will require review at a later date and an 'Analysis Plan' will be provided.

6.7. Blinding

Only the clinicians reviewing significant true event ECGs will be blind in this trial due to the equipment involved neither the patient or the physiologist can be blind.

All ILR follow-up appointments in CDDFT hospitals are carried out by a qualified Cardiac Physiologist. The physiologist reviews the stored data and prints relevant, significant findings for presentation to the Clinician. The software incorporated into the programmer and the Carelink™ system enable the data to be printed from the same printer. All patient identifiable information will be removed along with all information that can identify the follow-up origin of the data. The anonymised ECG data and appropriate medical history will be presented to the Clinician for evaluation. If a diagnosis is agreed on the basis of the ECG and medical history provided by the physiologist, then the patient will have reached their study endpoint and blinding can be removed. There will be no requirement for removal of blinding in emergency situations as patients can be treated in the normal way in these situations and interrogation carried out as soon as possible. It is important to note that only the evaluation of the data by the Clinician is blind.

7.0. Equipment
7.1. Equipment - Implanted

The ILRs to be used will be the Medtronic Reveal™ DX and XT. Both can manually store 3 recordings of 7 minutes and 30 seconds (6 minutes 30 seconds pre activation and 1 minute post activation) by use of the patient activator and can also record 27 automated recordings (30 seconds pre and 27 seconds post). Automated recordings are classified into 4 categories; Asystole, Bradycardia, Ventricular Tachycardia (VT) and Fast Ventricular Tachycardia (FVT). Once the memory is full the device will overwrite the oldest episode but can store a log of 30 of each type of event. At least 3 ECGs will be retained for each type of

automatic event. The Reveal™ XT can also distinguish AF events (Medtronic Inc, 2005; Medtronic Inc, 2010a; Medtronic Inc, 2010b).

7.2. Equipment – Follow Up

For the in office follow up a Medtronic 2090 Programmer for Medtronic implantable devices will be used. The header is placed over the device and uses telemetry to download the information stored on the ILR. The information downloaded is then displayed on the programmer where it can be reviewed, stored to disk or printed. The memory is then erased and ready to record until the next follow up (Medtronic Inc, 2009).

For remote follow up the patients will receive a Carelink™ home monitor which collects information via telemetry in the same way as the 2090 programmer and sends it over a standard telephone line to Medtronic's secured server that is accessed via a secure website. The information on the website can be accessed from any computer provided the authorised user details are used to log on (Medtronic inc, 2010a).

The primary server used for UK patients is located in the Netherlands in Maastricht. CDDFT personnel that are part of the patients direct care team have login credentials giving access to the patient's personal details. As part of the bi-directional information governance contract between CDDFT and Medtronic, patients are asked to sign an agreement which allows the sharing of their personal details by Medtronic. Medtronic will only share patient details with companies or contractors who require access in order to deliver Carelink™ services. Patients are also agreeing to their anonymised data to be used for analysis for the purposed of development. The current version of the Medtronic agreement , 'UK Version 4 DH Sept 2010 can be viewed in full in appendix 6

8.0. Ethical Considerations
8.1. Patient Involvement

The PIS has been reviewed informally by patients attending clinic. However it was decided that a formal arrangement for patient involvement was required.

A Patient Advisory Group (PAG) consisting of at least four patients will be formed. This group will consist of previous and current ILR patients both with and without Carelink™ experience. The PAG will be asked to review any changes to the PIS and supporting information. They will also be asked if they will assist with any patient concerns that may arise.

The members of the PAG will be chosen based on not only their expertise but also on the value it is felt that they will add to the study.

Letters will be sent to the proposed members of the PAG asking them if they would be interested in assisting with the study. If they would like to take part then they will be asked to attend a meeting at their local CDDFT hospital where they will be fully informed of the study and their role as a member of the PAG.

This meeting will be hosted by the CI who will also inform them that their involvement is entirely voluntary and they are free to leave the group at any time.

Currently there is no provision for financial gain for PAG members but travelling expenses for PAG duties such as meetings will be paid in line with current CDDFT allowances. Additionally refreshments will be provided at meetings.

Participants will also be given the contact details of an independent person that will be available to answer questions on research in general and mediate if the participant has any concerns that they do not wish to directly speak to a researcher about.

8.2. Ethics Committee Approval

The details of this research will be submitted to the regional NHS research ethics committee and Durham University's School of Medicine, Pharmacy and Health Sub-Ethics Committee for favourable opinion.

8.3. Patient Consent

Patients will be asked to give their consent for:

All data held on their device such as; Name, D.O.B, reason for implant and any ECGs stored to be stored on Medtronic's secure web-based server, along with their selected landline telephone number and address (Carelink™ arm patients only).
Their Medical records and device data to be accessed by the investigators of the study, for both research and follow-up purposes (all patients).
Their data to be anonymised by the Chief Investigator and added to the research database created for the trial (all patients).

8.4. Data Retention and Destruction

Patient identifiable data will be kept for no longer than three months after the trial is complete, except for the contact details of those patients that requested copies of publications arising from the study and / or final study reports. The data to be destroyed will be done so in accordance with the trusts destruction policy.

Research data that has been anonymised will be retained for up to ten years post completion of the study and will then be destroyed in line with the trusts destruction policy.

8.5. Trial Steering Group

A Multi Disciplinary Trial Steering Group (MDTSG) will be set up to monitor the conduct, safety and efficacy of the trial. The MDTSG will review the trial regularly and additionally the Chief Investigator will present aggregated

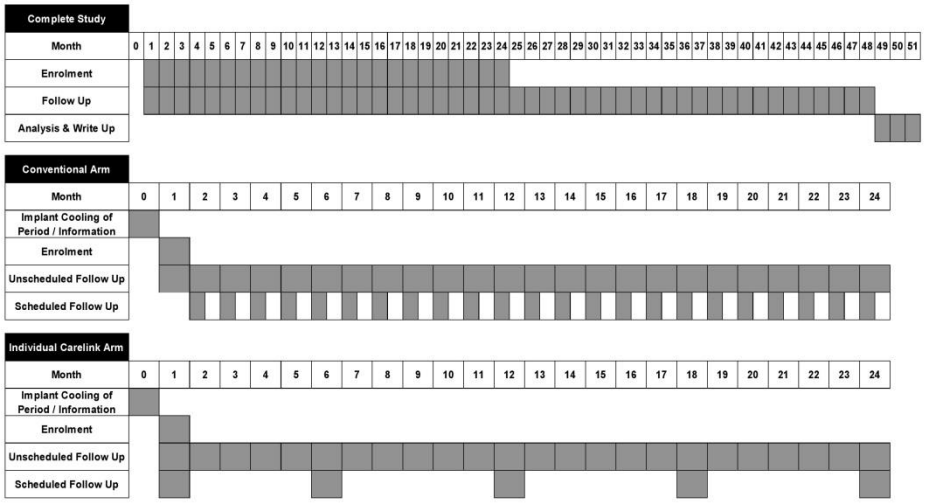
summary data to the MDTSG after the first 50 patients are enrolled and at 18 months.

The MDTSG will also be informed immediately of any complaints or issues that may arise and how the CI intends to resolve any such complaints or issues.

8.6. Study Timeline

Gantt chart 1 shows the study timeline, demonstrating the overall timeline for the study and the individual timelines for control and Carelink™ arm patients.

Diagram 1 – study timelines



9.0. Investigation Team

Chief Investigator – Gareth Pounds Cardiac Physiologist

Clinical Supervisors – Jane Curry Principal Cardiac Physiologist
Professor J.J. Murphy Consultant Cardiologist

Academic Supervisors – Professor A.P.S Hungin Head of School and Dean of Medicine
Dr Douglas Wilson Statistician

Researchers – Ruth Laity Senior Cardiac Physiologist
Paul Skinner Specialist Cardiac Physiologist
Christopher Cox Specialist Cardiac Physiologist

10.0. References

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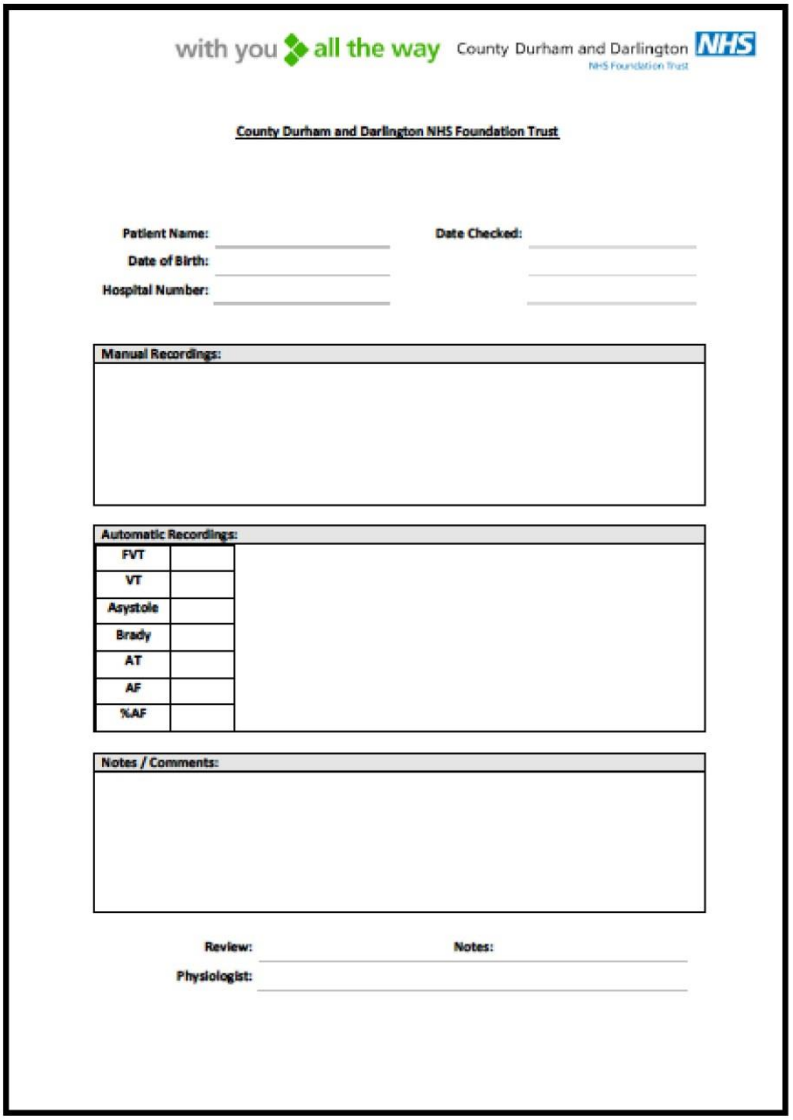
Appendix 1



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NHS Foundation Trust

County Durham and Darlington NHS Foundation Trust

Patient Name: _____ **Date Checked:** _____

Date of Birth: _____

Hospital Number: _____

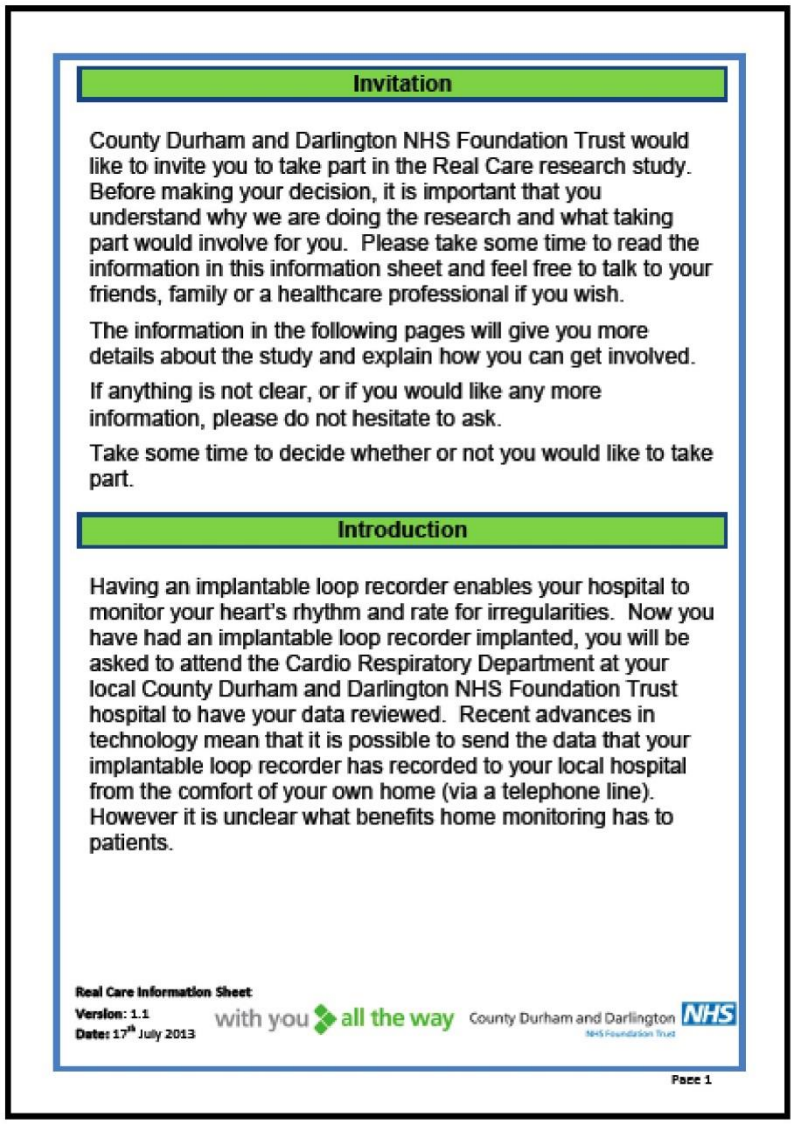
Manual Recordings:

Automatic Recordings:		
FVT		
VT		
Asystole		
Brady		
AT		
AF		
%AF		

Notes / Comments:

Review: _____ **Notes:** _____

Physiologist: _____



Invitation

County Durham and Darlington NHS Foundation Trust would like to invite you to take part in the Real Care research study. Before making your decision, it is important that you understand why we are doing the research and what taking part would involve for you. Please take some time to read the information in this information sheet and feel free to talk to your friends, family or a healthcare professional if you wish.

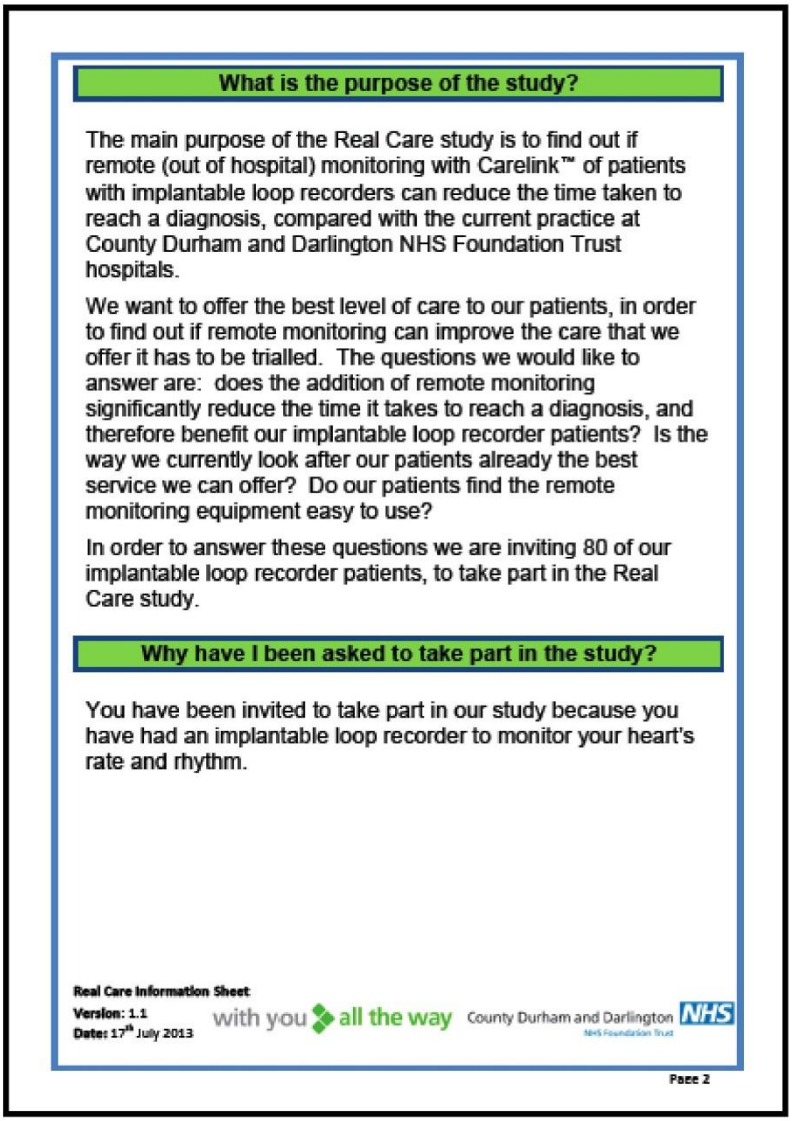
The information in the following pages will give you more details about the study and explain how you can get involved.

If anything is not clear, or if you would like any more information, please do not hesitate to ask.

Take some time to decide whether or not you would like to take part.

Introduction

Having an implantable loop recorder enables your hospital to monitor your heart's rhythm and rate for irregularities. Now you have had an implantable loop recorder implanted, you will be asked to attend the Cardio Respiratory Department at your local County Durham and Darlington NHS Foundation Trust hospital to have your data reviewed. Recent advances in technology mean that it is possible to send the data that your implantable loop recorder has recorded to your local hospital from the comfort of your own home (via a telephone line). However it is unclear what benefits home monitoring has to patients.



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We want to offer the best level of care to our patients, in order to find out if remote monitoring can improve the care that we offer it has to be trialled. The questions we would like to answer are: does the addition of remote monitoring significantly reduce the time it takes to reach a diagnosis, and therefore benefit our implantable loop recorder patients? Is the way we currently look after our patients already the best service we can offer? Do our patients find the remote monitoring equipment easy to use?

In order to answer these questions we are inviting 80 of our implantable loop recorder patients, to take part in the Real Care study.

Why have I been asked to take part in the study?

You have been invited to take part in our study because you have had an implantable loop recorder to monitor your heart's rate and rhythm.

Do I have to take part?

No. It is your choice whether to take part or not. If you decide to take part, whilst we would appreciate you seeing the study through to completion, there is no obligation and you would be free to withdraw at any point, without explanation and with no bearing whatsoever on the care that you would continue to receive from the trust's healthcare professionals. If you did wish to leave the study, simply contact your local Cardio Respiratory Department research team or our Chief Investigator and let them know that you wish to withdraw. Contact Details can be found at the rear of this information sheet.

What does taking part in the real care study involve?

All participants in this study will have given their consent voluntarily, understanding that they may be required to take part for a maximum of two years. If you join the study you will be asked to either, send data from your implantable loop recorder on a regular basis via a special piece of equipment (Carelink™) that will be sent to you through the post, or you may be required to attend appointments in your Cardiology Department at six month intervals (current standard practice). You will be assigned to the Carelink™ or standard practice groups at random, meaning that you have a 50% chance of being in either group. This process of randomisation is carried out by an independent person and none of the research staff can influence the process.

Randomisation is carried out in this way to ensure that entry into the study is carried out fairly for all patients.

If you are using the Carelink™ remote monitoring system, you will be asked to fill out a questionnaire designed to assess the equipment and our staff. The questionnaire will be sent to your home address along with a prepaid return envelope, after you have been involved in the study for three months.

How can I get involved in the study?

If you decide that you would like to participate in the study you will have the opportunity to get involved at your first follow up appointment. You will be given the chance to ask any questions that you may have, then if everything is in order and you are happy to move forward you will be asked to sign a consent form and you will be randomly assigned to your study group.

How does my information get to my hospital?

If you are in the Carelink™ remote monitoring section of the study you will be asked to send a transmission every two weeks. In order to do this you will be given a demonstration of the equipment and a kit will be sent directly to your home address. The equipment is small and lightweight, approximately the size of a small freeview box.

Sending transmissions takes around 5 minutes, the Carelink™ equipment reads the data from your device and sends it to a secure website using a free phone number (there is no additional cost to you). The staff at your local CDDFT hospital will then look at your data by logging on to the website with a personal username and password known only by them. Once the data has been reviewed, you will receive a call to let you know what we found and to ask if you have had any problems.

You can send you transmissions at any time on your scheduled day when it is convenient for you, additional transmissions can be sent at any time if you have used the manual activator (given to you on the day of implant) to record manually.

What are the risks of taking part?

There are no known additional risks to taking part in the study, but if we were to be made aware of any during the course of the study we would contact you immediately so that we can discuss whether you would like to continue taking part.

What are the benefits of taking part?

The information gained from this study will be used to ensure that future implantable loop recorder patients not just within our hospitals but also worldwide, receive the best possible care.

How long is my data collected for?

Your data will be collected for up to two years, we will stop collecting data before that point if you receive a diagnosis or have your device removed prematurely for any reason. Premature reasons for removal would be due to complications that will have been explained to you before the implant, or because you have requested for the device to be removed. In some cases a diagnosis may be made but the device will be left in so that we can monitor how well you respond to treatment. If your device is left in you will be offered to continue on the same method of follow-up but your data after diagnosis will no longer be entered into the study.

What happens at the end of the study?

When the research study finishes we will inform you of the results if you wish to see them. We will also publish the results in a professional medical journal as soon as possible after the study finishes. You would not be identified personally in any published report.

Will my information be kept confidential?

Only staff within the County Durham and Darlington NHS Foundation Trust and Medtronic (if you are on Carelink™) will have access to your identifiable information and all information will be handled in the strictest of confidence for medical, research, audit and regulatory purposes.

If you are using Carelink™ your contact details will also be passed to the delivery company that is delivering you Carelink™ equipment.

The personal identifiable data collected will include your name, date of birth, address and telephone number.

Who has reviewed this study?

Durham University's School of Medicine, Pharmacy and Health Sub-Ethics Committee, County Durham and Darlington NHS foundation Trust Research Review Board and the Regional NHS Ethics committee have reviewed this study for compliance with medical and ethical standards and scientific value and has given a favourable ethical opinion for conduct in the NHS.

Contact Details

Chief Research Investigator

Gareth Pounds Cardiac Physiologist
Darlington Memorial Hospital
Hollyhurst Road, Darlington, DL3 6HX

Phone: 01325 743154 Email: gareth.pounds@cddft.nhs.uk

Research Team Numbers

Research Team Darlington Memorial Hospital
Phone: 01325 743154

Research Team University Hospital North Durham
Phone: 0191 3332196

Research Team Bishop Auckland General Hospital
Phone: 01388 455512

Clinical Supervisors

Professor Jerry Murphy Consultant Cardiologist
Phone 01325 380100 Email: jerry.murphy@cddft.nhs.uk

Jane Curry Head of Cardiac and Respiratory Services
Phone 01325 743154 Email: jane.curry@cddft.nhs.uk

For independent information regarding research or participation in research please contact:

Lynne Williams, Research and Development Manager
Phone: 01325 743737 Email: lynne.williams@cddft.nhs.uk

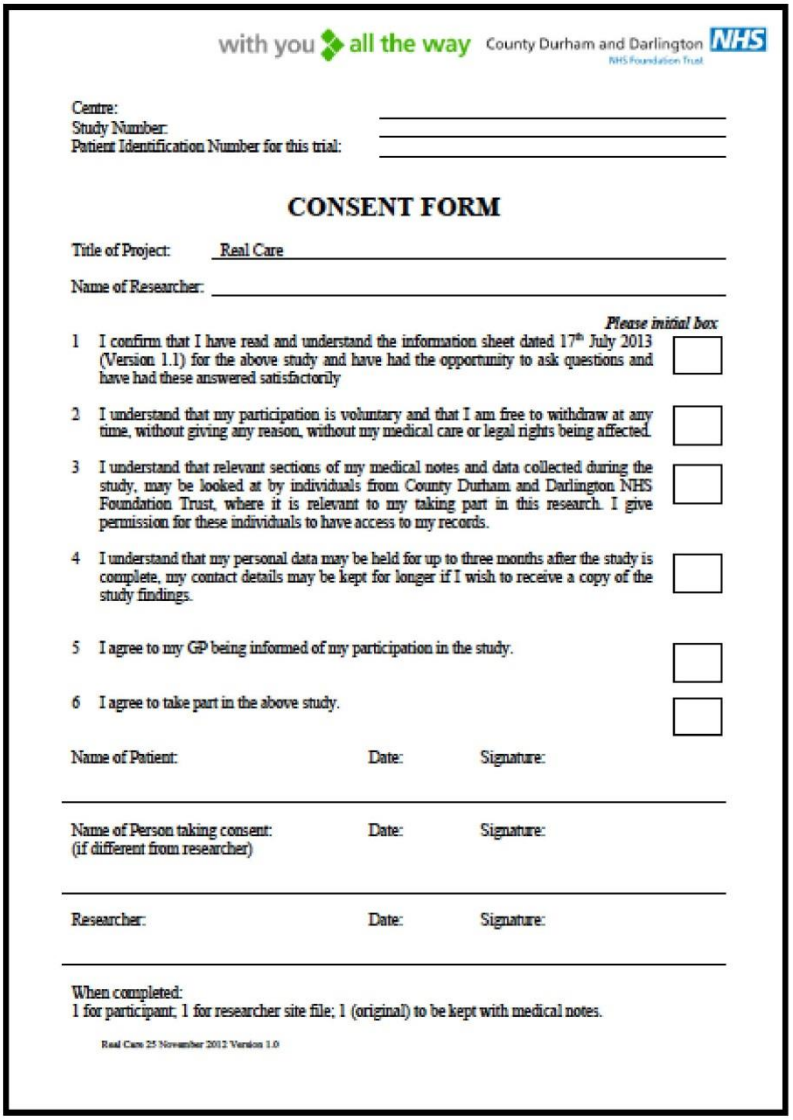
For any other independent advice or information contact:

Patient Experience Team
Darlington Memorial Hospital
Hollyhurst Road, Darlington, DL3 6HX
Phone: 0800 783 5774 Email: patient.experience@cddft.nhs.uk

Technical / Equipment Support

If you have any issues with the Carelink™ equipment contact the Chief Investigator or one of the Research teams who will be happy to assist you in resolving the problem.

Appendix 3



with you all the way County Durham and Darlington NHS
NHS Foundation Trust

Centre:
Study Number:
Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Real Care

Name of Researcher:

Please initial box

1 I confirm that I have read and understand the information sheet dated 17th July 2013 (Version 1.1) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily ☐

2 I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3 I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from County Durham and Darlington NHS Foundation Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4 I understand that my personal data may be held for up to three months after the study is complete, my contact details may be kept for longer if I wish to receive a copy of the study findings. ☐

5 I agree to my GP being informed of my participation in the study. ☐

6 I agree to take part in the above study. ☐

Name of Patient: Date: Signature:

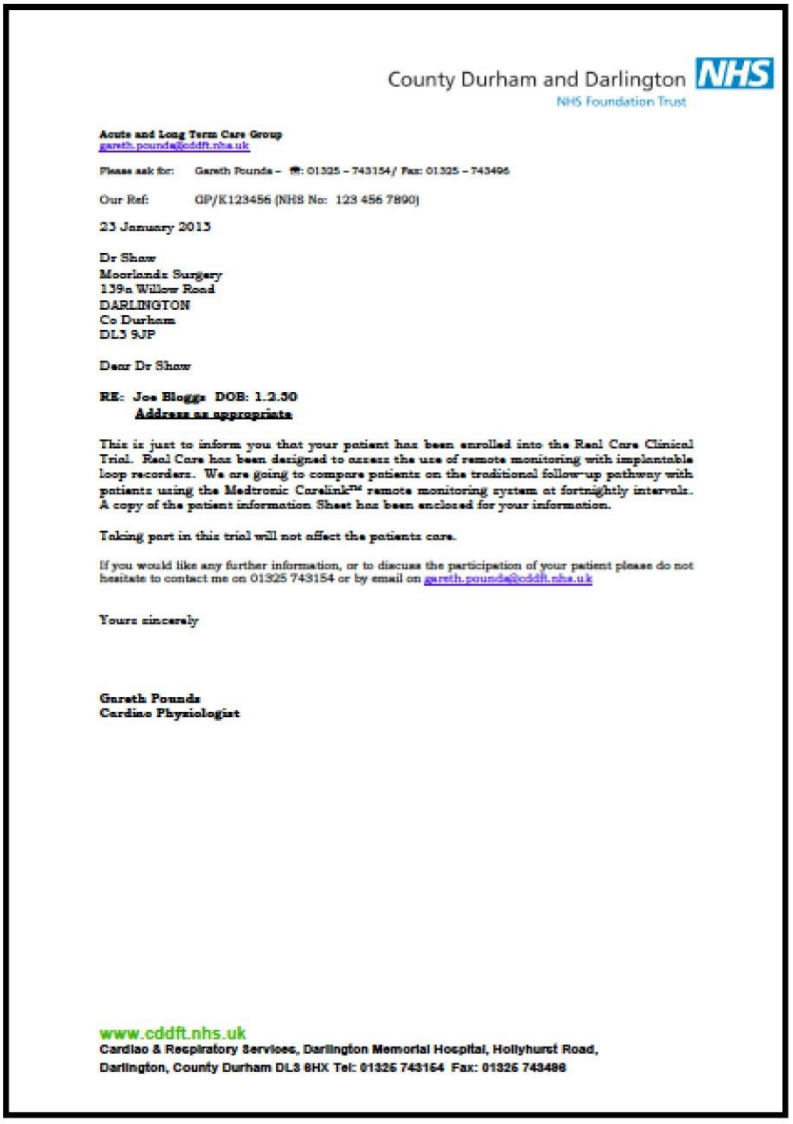
Name of Person taking consent: (if different from researcher) Date: Signature:

Researcher: Date: Signature:

When completed:
1 for participant; 1 for researcher site file; 1 (original) to be kept with medical notes.

Real Care 25 November 2012 Version 1.0

Appendix 4



County Durham and Darlington NHS
NHS Foundation Trust

Acute and Long Term Care Group
gareth.pounds@cddft.nhs.uk

Please ask for: Gareth Founds – ☎: 01325 – 743154/ Fax: 01325 – 743496

Our Ref: GP/K123456 (NHS No: 123 456 7890)

23 January 2013

Dr Show
Moorlands Surgery
139a Willow Road
DARLINGTON
Co Durham
DL3 9JP

Dear Dr Show

RE: Joe Bloggs DOB: 1.2.50
Address as appropriate

This is just to inform you that your patient has been enrolled into the Real Care Clinical Trial. Real Care has been designed to assess the use of remote monitoring with implantable loop recorders. We are going to compare patients on the traditional follow-up pathway with patients using the Medtronic Carelink™ remote monitoring system at fortnightly intervals. A copy of the patient information Sheet has been enclosed for your information.

Taking part in this trial will not affect the patients care.

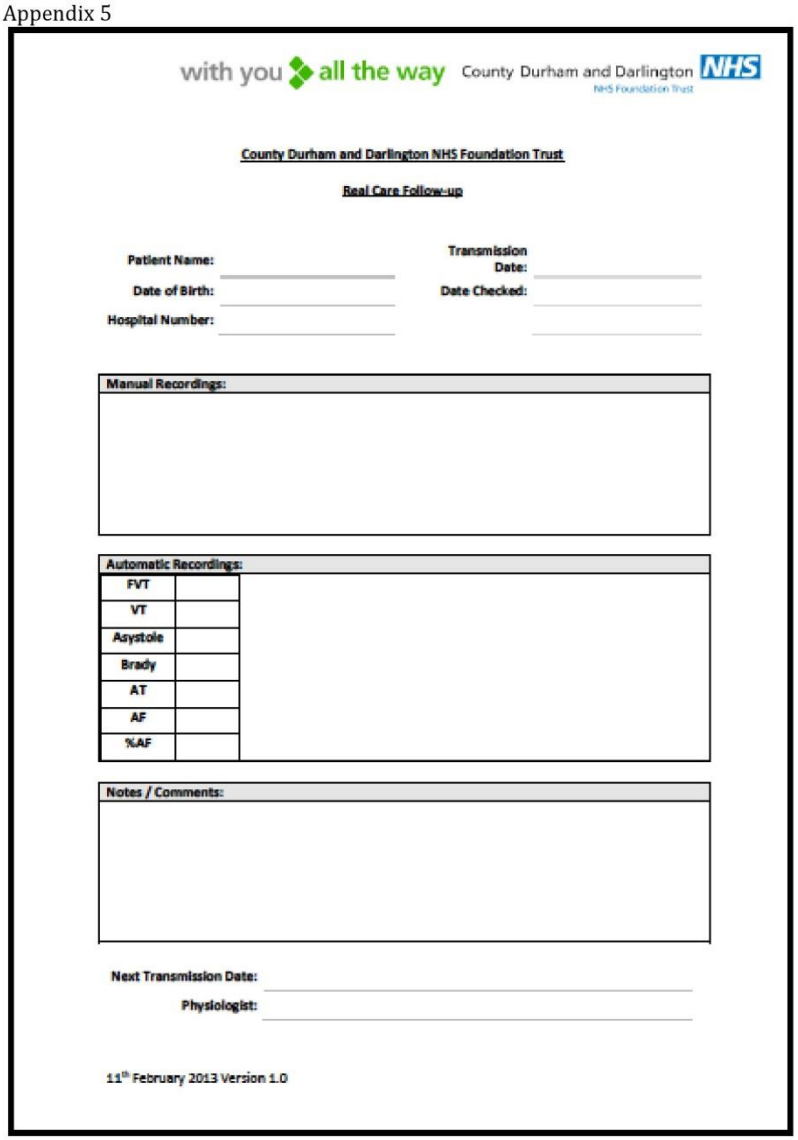
If you would like any further information, or to discuss the participation of your patient please do not hesitate to contact me on 01325 743154 or by email on gareth.pounds@cddft.nhs.uk

Yours sincerely

Gareth Pounds
Cardiac Physiologist

www.cddft.nhs.uk
Cardiac & Respiratory Services, Darlington Memorial Hospital, Hollyhurst Road, Darlington, County Durham DL3 6HX Tel: 01325 743154 Fax: 01325 743496

Appendix 5



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NHS Foundation Trust

County Durham and Darlington NHS Foundation Trust

Real Care Follow-up

Patient Name: _____ **Transmission Date:** _____

Date of Birth: _____ **Date Checked:** _____

Hospital Number: _____

Manual Recordings:

Automatic Recordings:	
FVT	
VT	
Asystole	
Brady	
AT	
AF	
%AF	

Notes / Comments:

Next Transmission Date: _____

Physiologist: _____

11th February 2013 Version 1.0

Appendix 6

Statement of Privacy Principles for Patients using the Medtronic CareLink® Services in UK

Your doctor has provided you with information about Medtronic CareLink® Services provided by Medtronic Limited. CareLink is an internet-based service, which allows your physician to remotely monitor your implantable cardiac device by interrogating, collecting and transmitting implanted cardiac device and patient data.

The Services allow that the information of your Medtronic implantable cardiac device (the "Device") can be stored in Medtronic CareLink® Network ("Network") and can be processed to improve your care or to develop new products and services that you and other patients could benefit from. It is also possible that other information coming from other forms or health data sources (i.e. weight scales, blood pressure monitors, etc) could be also imported in the Network to make this information also available for processing. It is expected that in the future, with your additional consent, your physician could remotely program some parameters of your device to improve your care.

The Hospital responsible for the monitoring of your implantable cardiac device is responsible for the personal data collected and processed by Medtronic when supplying the CareLink® Services. In order to regulate the collection and processing of personal data, the hospital and Medtronic have entered into an agreement as required according to applicable data protection law.

The personal data which will be processed in connection with the provision of the CareLink® Services will be collected from you, your physician, your medical records and your implantable cardiac device. The personal data includes medical and technical data, your name, address, telephone number.

Medtronic will not keep personal data for any longer than necessary and uses all reasonably necessary safeguards required under applicable law in order to protect your personal data. Only employees and contractors of Medtronic who needs to have access to personal data in order to carry out the CareLink® Services will be granted access. This may include transfer of personal data to other countries, recognized by the European Union as having adequate privacy protection. Medtronic will only transfer personal data to other areas than such countries or territories if the information will be adequately protected, by contract or otherwise, or if Medtronic is permitted to do so.

Medtronic shares personal data with companies which Medtronic hires in order to perform parts of the CareLink Services, for example monitor shipment. Those third parties are obligated to process the personal data in accordance with the principles of this document.

Medtronic reserves the right to use the data, after anonymisation, for analysis, in order to develop and improve medical programs, therapies, services and products. Upon the request of the Medical Centre, Medtronic may carry out customized analysis of your data stored in the devices together with the relevant clinical information that the Medical Centre deems necessary for such analysis. The outcome will only be communicated to the Medical Centre.

You may request access to your personal data and information on how Medtronic processes your data. Please contact your physician to receive that information. You also have a right to request that personal data which you consider as incorrect or incomplete is corrected.

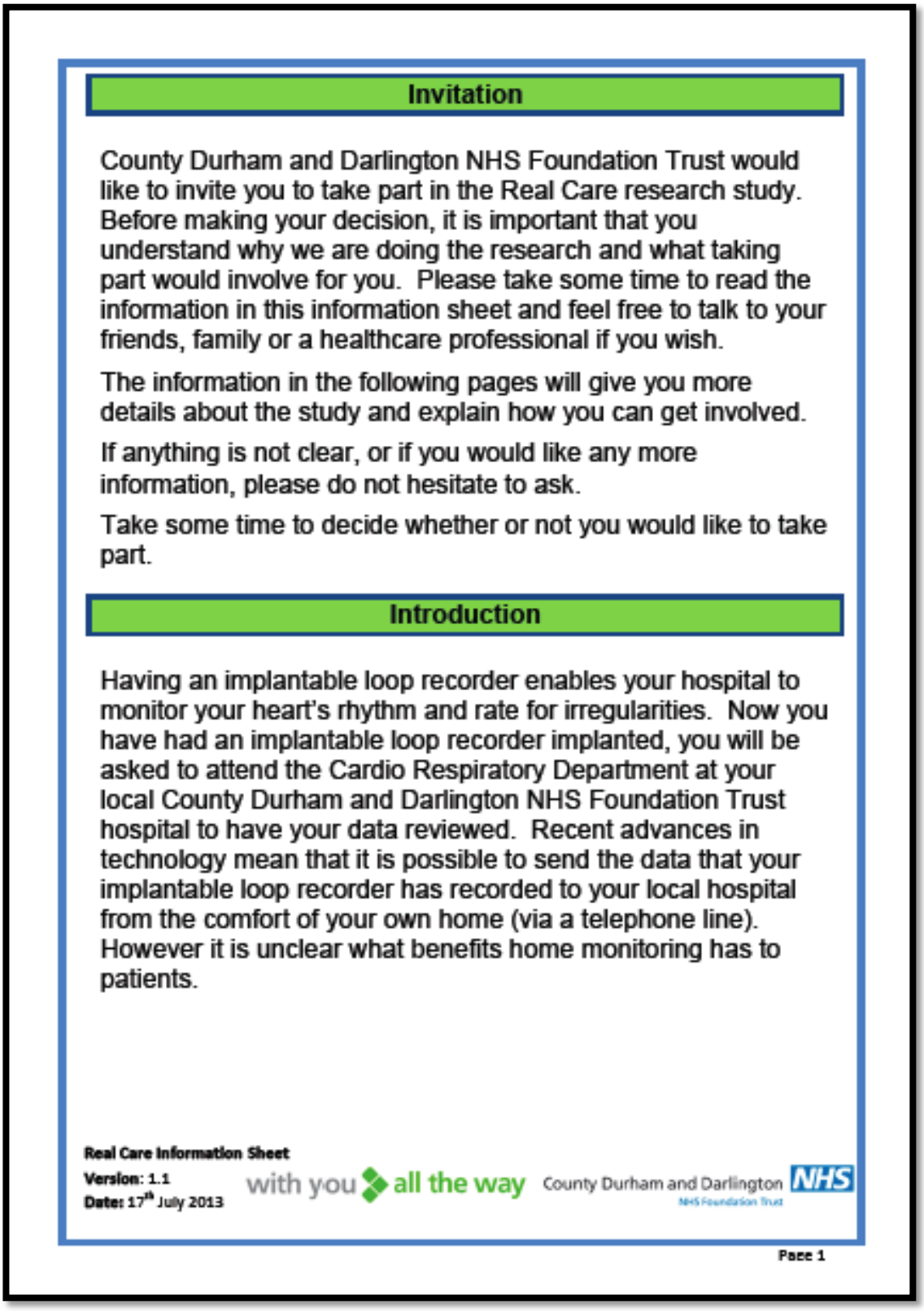
It is important that you read and understand this document. If there is anything in this document that you do not understand please discuss this with your physician before signing the consent. By signing this document, you give your consent to the collecting, processing and use of your personal data as set out in this document. You may refuse participation or you may stop participation in the CareLink® Services at any time without affecting the quality of your health care or the relationship with your physician. I agree I have been fully instructed on the CareLink Monitor and am comfortable with how to use it.

The patient's signature

Date (to be filled out by the patient)

UK Version 4 DH Sept 2010

Appendix 2 - Patient Information Sheet (PIS)



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How does my information get to my hospital?

If you are in the Carelink™ remote monitoring section of the study you will be asked to send a transmission every two weeks. In order to do this you will be given a demonstration of the equipment and a kit will be sent directly to your home address. The equipment is small and lightweight, approximately the size of a small freeview box.

Sending transmissions takes around 5 minutes, the Carelink™ equipment reads the data from your device and sends it to a secure website using a free phone number (there is no additional cost to you). The staff at your local CDDFT hospital will then look at your data by logging on to the website with a personal username and password known only by them. Once the data has been reviewed, you will receive a call to let you know what we found and to ask if you have had any problems.

You can send you transmissions at any time on your scheduled day when it is convenient for you, additional transmissions can be sent at any time if you have used the manual activator (given to you on the day of implant) to record manually.

What are the risks of taking part?

There are no known additional risks to taking part in the study, but if we were to be made aware of any during the course of the study we would contact you immediately so that we can discuss whether you would like to continue taking part.

What are the benefits of taking part?

The information gained from this study will be used to ensure that future implantable loop recorder patients not just within our hospitals but also worldwide, receive the best possible care.

How long is my data collected for?

Your data will be collected for up to two years, we will stop collecting data before that point if you receive a diagnosis or have your device removed prematurely for any reason. Premature reasons for removal would be due to complications that will have been explained to you before the implant, or because you have requested for the device to be removed. In some cases a diagnosis may be made but the device will be left in so that we can monitor how well you respond to treatment. If your device is left in you will be offered to continue on the same method of follow-up but your data after diagnosis will no longer be entered into the study.

What happens at the end of the study?

When the research study finishes we will inform you of the results if you wish to see them. We will also publish the results in a professional medical journal as soon as possible after the study finishes. You would not be identified personally in any published report.

Will my information be kept confidential?

Only staff within the County Durham and Darlington NHS Foundation Trust and Medtronic (if you are on Carelink™) will have access to your identifiable information and all information will be handled in the strictest of confidence for medical, research, audit and regulatory purposes.

If you are using Carelink™ your contact details will also be passed to the delivery company that is delivering you Carelink™ equipment.

The personal identifiable data collected will include your name, date of birth, address and telephone number.

Who has reviewed this study?

Durham University's School of Medicine, Pharmacy and Health Sub-Ethics Committee, County Durham and Darlington NHS foundation Trust Research Review Board and the Regional NHS Ethics committee have reviewed this study for compliance with medical and ethical standards and scientific value and has given a favourable ethical opinion for conduct in the NHS.

Contact Details

Chief Research Investigator

Gareth Pounds Cardiac Physiologist
Darlington Memorial Hospital
Hollyhurst Road, Darlington, DL3 6HX

Phone: 01325 743154 Email: gareth.pounds@cddft.nhs.uk

Research Team Numbers

Research Team Darlington Memorial Hospital
Phone: 01325 743154

Research Team University Hospital North Durham
Phone: 0191 3332196

Research Team Bishop Auckland General Hospital
Phone: 01388 455512

Clinical Supervisors

Professor Jerry Murphy Consultant Cardiologist
Phone 01325 380100 Email: jerry.murphy@cddft.nhs.uk

Jane Curry Head of Cardiac and Respiratory Services
Phone 01325 743154 Email: jane.curry@cddft.nhs.uk

For independent information regarding research or participation in research please contact:

Lynne Williams, Research and Development Manager
Phone: 01325 743737 Email: lynne.williams@cddft.nhs.uk

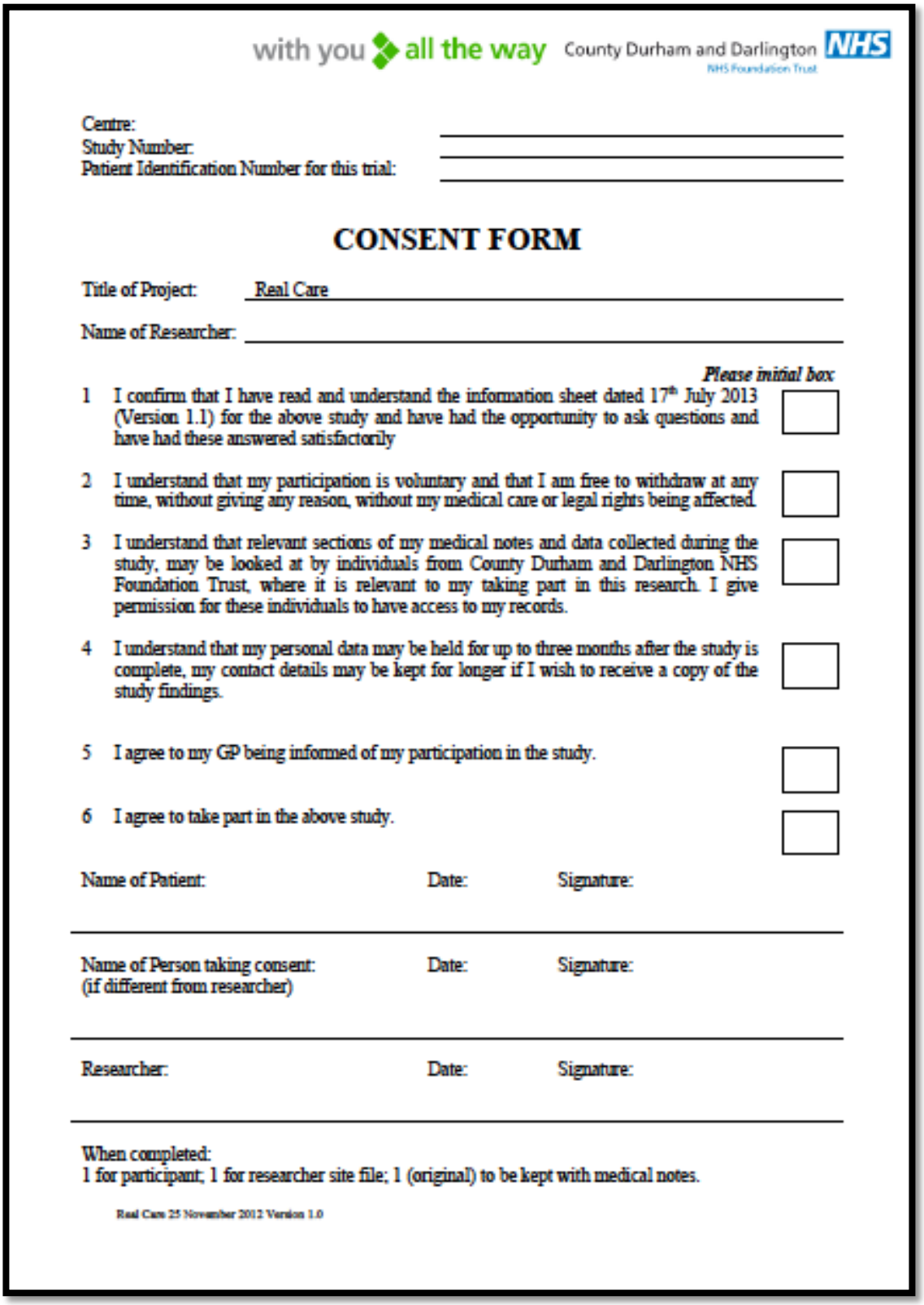
For any other independent advice or information contact:

Patient Experience Team
Darlington Memorial Hospital
Hollyhurst Road, Darlington, DL3 6HX
Phone: 0800 783 5774 Email: patient.experience@cddft.nhs.uk

Technical / Equipment Support

If you have any issues with the Carelink™ equipment contact the Chief Investigator or one of the Research teams who will be happy to assist you in resolving the problem.

Appendix 3 - Real Care consent form



with you all the way County Durham and Darlington NHS
NHS Foundation Trust

Centre: _____
Study Number: _____
Patient Identification Number for this trial: _____

CONSENT FORM

Title of Project: Real Care

Name of Researcher: _____

Please initial box

1 I confirm that I have read and understand the information sheet dated 17th July 2013 (Version 1.1) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily ☐

2 I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3 I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from County Durham and Darlington NHS Foundation Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4 I understand that my personal data may be held for up to three months after the study is complete, my contact details may be kept for longer if I wish to receive a copy of the study findings. ☐

5 I agree to my GP being informed of my participation in the study. ☐

6 I agree to take part in the above study. ☐

Name of Patient: Date: Signature:

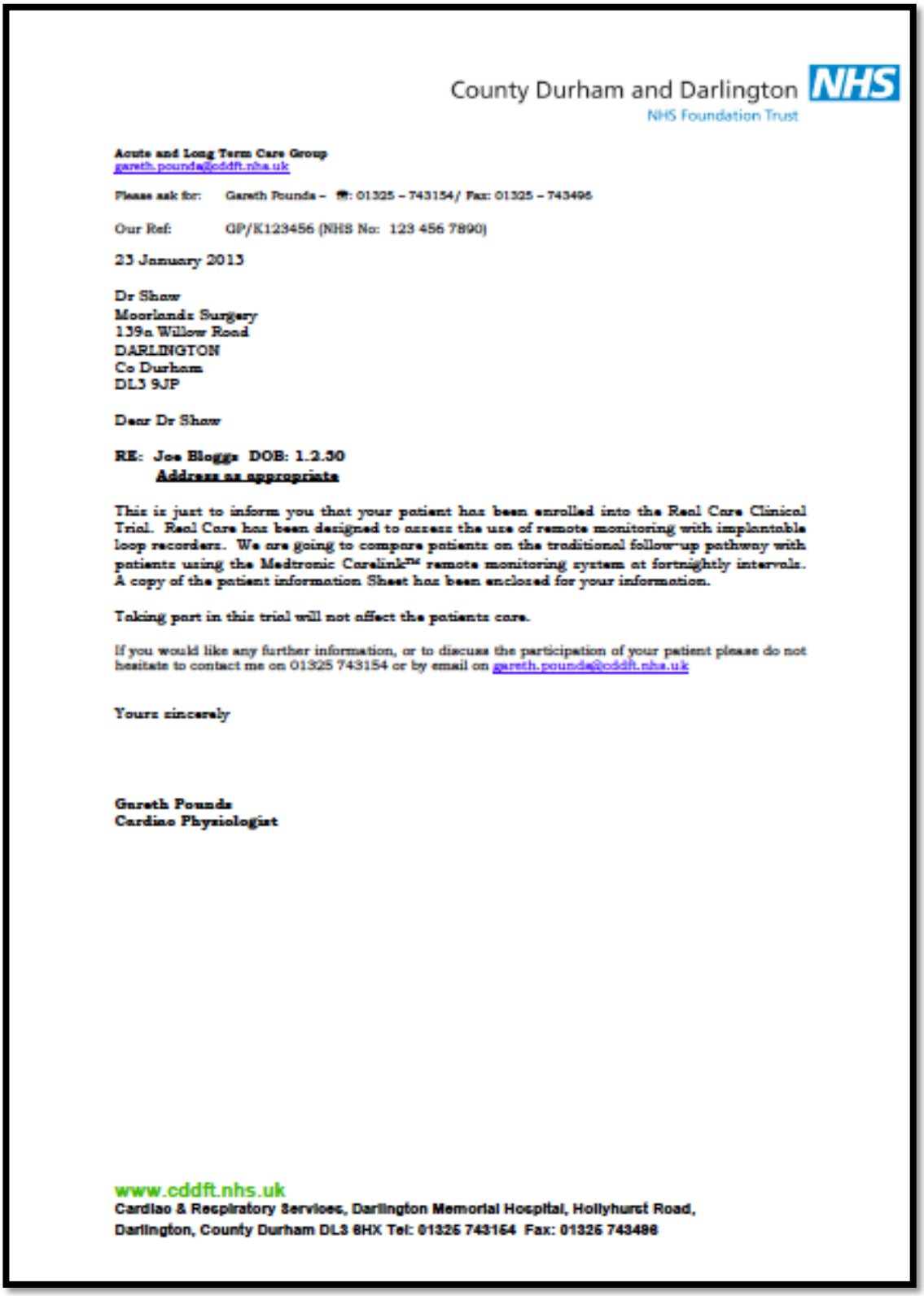
Name of Person taking consent: (if different from researcher) Date: Signature:

Researcher: Date: Signature:

When completed:
1 for participant; 1 for researcher site file; 1 (original) to be kept with medical notes.

Real Care 25 November 2012 Version 1.0

Appendix 4 - Real Care GP letter



County Durham and Darlington NHS
NHS Foundation Trust

Acute and Long Term Care Group
gareth.pounds@cddft.nhs.uk

Please ask for: Gareth Pounds – ☎: 01325 – 743154/ Fax: 01325 – 743496

Our Ref: GP/K123456 (NHS No: 123 456 7890)

23 January 2013

Dr Shaw
Moorlands Surgery
139a Willow Road
DARLINGTON
Co Durham
DL3 9JP

Dear Dr Shaw

RE: Joe Bloggs DOB: 1.2.50
Address as appropriate

This is just to inform you that your patient has been enrolled into the Real Care Clinical Trial. Real Care has been designed to assess the use of remote monitoring with implantable loop recorders. We are going to compare patients on the traditional follow-up pathway with patients using the Medtronic Carelink™ remote monitoring system at fortnightly intervals. A copy of the patient information Sheet has been enclosed for your information.

Taking part in this trial will not affect the patients care.

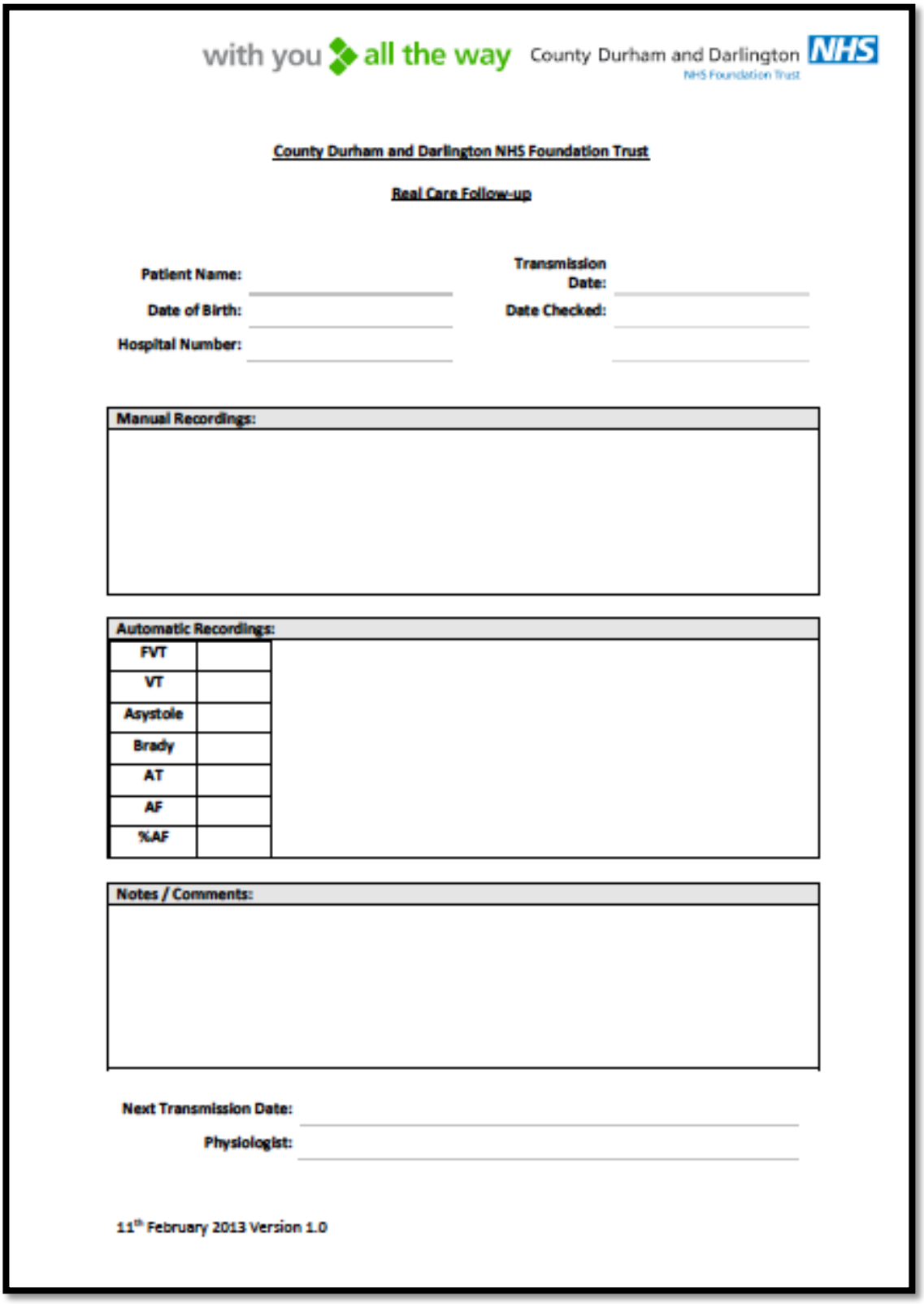
If you would like any further information, or to discuss the participation of your patient please do not hesitate to contact me on 01325 743154 or by email on gareth.pounds@cddft.nhs.uk

Yours sincerely

Gareth Pounds
Cardiac Physiologist

www.cddft.nhs.uk
Cardiac & Respiratory Services, Darlington Memorial Hospital, Hollyhurst Road, Darlington, County Durham DL3 6HX Tel: 01325 743164 Fax: 01325 743496

Appendix 5 - Real Care follow - up form



with you all the way County Durham and Darlington NHS
NHS Foundation Trust

County Durham and Darlington NHS Foundation Trust

Real Care Follow-up

Patient Name: _____ **Transmission Date:** _____

Date of Birth: _____ **Date Checked:** _____

Hospital Number: _____

Manual Recordings:

Automatic Recordings:		
FVT		
VT		
Asystole		
Brady		
AT		
AF		
%AF		

Notes / Comments:

Next Transmission Date: _____

Physiologist: _____

11th February 2013 Version 1.0

Appendix 6 - Medtronic Carelink™ consent form

Medtronic

Statement of Privacy Principles for Patients using the Medtronic CareLink® Services in UK

Your doctor has provided you with information about Medtronic CareLink® Services provided by Medtronic Limited. CareLink is an internet-based service, which allows your physician to remotely monitor your implantable cardiac device by interrogating, collecting and transmitting implanted cardiac device and patient data.

The Services allow that the information of your Medtronic implantable cardiac device (the "Device") can be stored in Medtronic CareLink® Network ("Network") and can be processed to improve your care or to develop new products and services that you and other patients could benefit from. It is also possible that other information coming from other forms or health data sources (i.e. weight scales, blood pressure monitors, etc) could be also imported in the Network to make this information also available for processing. It is expected that in the future, with your additional consent, your physician could remotely program some parameters of your device to improve your care.

The Hospital responsible for the monitoring of your implantable cardiac device is responsible for the personal data collected and processed by Medtronic when supplying the CareLink® Services. In order to regulate the collection and processing of personal data, the hospital and Medtronic have entered into an agreement as required according to applicable data protection law.

The personal data which will be processed in connection with the provision of the CareLink® Services will be collected from you, your physician, your medical records and your implantable cardiac device. The personal data includes medical and technical data, your name, address, telephone number.

Medtronic will not keep personal data for any longer than necessary and uses all reasonably necessary safeguards required under applicable law in order to protect your personal data. Only employees and contractors of Medtronic who needs to have access to personal data in order to carry out the CareLink® Services will be granted access. This may include transfer of personal data to other countries, recognized by the European Union as having adequate privacy protection. Medtronic will only transfer personal data to other areas than such countries or territories if the information will be adequately protected, by contract or otherwise, or if Medtronic is permitted to do so.

Medtronic shares personal data with companies which Medtronic hires in order to perform parts of the CareLink Services, for example monitor shipment. Those third parties are obligated to process the personal data in accordance with the principles of this document.

Medtronic reserves the right to use the data, after anonymisation, for analysis, in order to develop and improve medical programs, therapies, services and products. Upon the request of the Medical Centre, Medtronic may carry out customized analysis of your data stored in the devices together with the relevant clinical information that the Medical Centre deems necessary for such analysis. The outcome will only be communicated to the Medical Centre.

You may request access to your personal data and information on how Medtronic processes your data. Please contact your physician to receive that information. You also have a right to request that personal data which you consider as incorrect or incomplete is corrected.

It is important that you read and understand this document. If there is anything in this document that you do not understand please discuss this with your physician before signing the consent. By signing this document, you give your consent to the collecting, processing and use of your personal data as set out in this document. You may refuse participation or you may stop participation in the CareLink® Services at any time without affecting the quality of your health care or the relationship with your physician. I agree I have been fully instructed on the CareLink Monitor and am comfortable with how to use it.

The patient's signature

Date (to be filled out by the patient)

UK Version 4 DH Sept 2010